1,3-Dipolar Character of Six-membered Aromatic Rings. Part 44.[1] Further Examples of Troponoid Synthesis

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Adducts formed from 3-hydroxypyridine and two moles of the dipolarophiles, acrylonitrile and methyl acrylate, are converted by quaternisation and Hofmann elimination into 4-cyanotropolone and 4-methoxycarbonyltropolone. Overall yields of *ca.* 25% are achieved in one-pot reactions from 3-hydroxypyridine. 2-Chloro-, 2-bromo-, and 2-cyano-1-methyl-3-oxidopyridinium form adducts with 2π addends, some of which were converted into tropone derivatives.

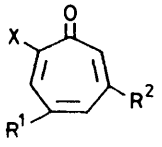
SEVERAL synthetic methods for tropones and tropolones have been developed in recent years. Ring expansions of benzenoid compounds by carbanoids yield benzotropones.[2-4]

Dehalogenation of αα-dibromoketones with iron carbonyls in the presence of 1,3-dienes gives cycloheptenones converted by bromination and dehydrobromination to various substituted tropones.[5] A versatile method [6] for tropolone synthesis involves the cycloaddition of cyclopentadiene followed by acetolysis. Troponoids are useful precursors [7] for azulenes. The growing interest of troponoids in theoretical,[8] photochemical,[9] and natural product [10] chemistry prompted us to reinvestigate their synthesis.

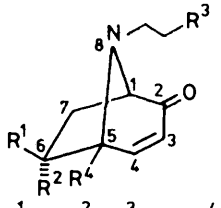
We have previously described the synthesis of 4-substituted troponoids [11] (1)—(4) and a 4-substituted 6-aryltropolone [12] (5) *via* Hofmann degradation of cycloadducts derived from 1-methyl- and 5-aryl-1-methyl-3-oxidopyridinium, respectively. A more economical and convenient synthesis of 4-substituted troponoids would involve the use of cycloadducts of the type (8)—(11) prepared directly from the reaction [13] between 3-hydroxypyridine and dipolarophiles. Although these cycloadducts (8)—(11) are unreactive towards MeI and Me_2SO_4, silver perchlorate–methyl iodide [14] readily converts them into the corresponding methyl perchlorates (14)—(17).

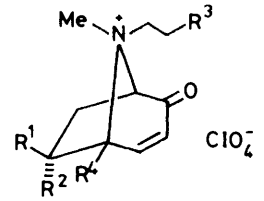
The stereochemistry at the bridgehead nitrogen of these quaternary salts was established by nuclear Overhauser experiments in which enhancement of the methyl singlet was observed on saturation of H-6-*exo* or H-7-*exo* signals. Thus quaternisation of the cycloadduct bridgehead nitrogen by methyl perchlorate occurs preferentially in the equatorial position, which result is analogous to those of Fodor *et al.*[15] and Supple and Eklum (Scheme 1).[16] Conventional Hofmann degradation using $NaHCO_3$ gave the troponoids (6) and (7) and the tropolones (1) and (2) in yields which depended on the time, temperature, and nature of the base.

The overall yields (with respect to 3-hydroxypyridine) of 4-cyanotropone and 4-methoxycarbonyltropone were 25% in one-pot reactions or 12 and 8%, respectively, overall. These yields compare favourably with the overall yields obtained from 1-methyl-3-oxidopyridinium described earlier [11] in this series. The method herein described involves a sequence of only three steps which is an advantage over the five-step sequence required for the 1-methyl-3-oxidopyridinium method. All three steps in the present synthesis can be executed in one reaction vessel without the necessity of isolating the intermediate products as in other tropone syntheses.[11]



(1) X = OH, R^1 = CN, R^2 = H
(2) X = OH, R^1 = CO_2Me, R^2 = H
(3) X = NMe_2, R^1 = CN, R^2 = H
(4) X = NMe_2, R^1 = CO_2Me, R^2 = H
(5) X = OH, R^1 = CN, R^2 = aryl
(6) X = $MeN(CH_2)_2CN$, R^1 = CN, R^2 = H
(7) X = $MeN(CH_2)_2CO_2Me$, R^1 = CO_2Me, R^2 = H





(8) R^1 = H, R^2 = R^3 = CN, R^4 = H
(9) R^2 = H, R^1 = R^3 = CN, R^4 = H
(10) R^2 = H, R^1 = R^3 = CO_2Me, R^4 = H
(11) R^1 = H, R^2 = R^3 = CO_2Me, R^4 = H
(12) R^1 = H, R^2 = R^3 = CN, R^4 = Me
(13) R^2 = H R^1 = R^3 = CN, R^4 = Me

(14) R^1 = H, R^2 = R^3 = CN, R^4 = H
(15) R^2 = H, R^1 = R^3 = CN, R^4 = H
(16) R^2 = H, R^1 = R^3 = CO_2Me, R^4 = H
(17) R^1 = H, R^2 = R^3 = CO_2Me, R^4 = H

SCHEME 1

As in the case of 3-hydroxypyridine,[13] 3-hydroxy-6-methylpyridine reacted with two moles of acrylonitrile to yield a mixture of *endo*- and *exo*-adducts (12) and (13): quaternisation of these proved unsuccessful. With methyl acrylate, no adduct was formed probably because of steric hindrance.

Attempted Alternative Troponoid Syntheses.—Cycloadducts possessing a 6-t-butoxycarbonyl group should readily lose isobutene. The resulting 6-carboxylic

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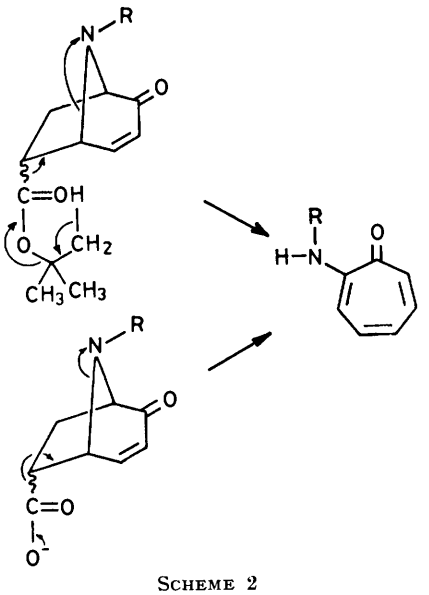
acid could undergo a Grob-type fragmentation to the corresponding 2-substituted aminotropones (Scheme 2).

3-Hydroxypyridine and t-butyl acrylate produced a mixture of the 6-*endo*- and 6-*exo*-adducts (18) and (21). The dimer [17] of 1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-3-oxidopyridinium (26) similarly yielded both the 6-*endo*- and the 6-*exo*-cycloadducts (19) and (22). Similarly, 1-(4-bromobenzoylvinyl)-3-oxidopyridinium (25), prepared [18] from the corresponding salt (24), gave an isomeric mixture of 6-*endo*- and 6-*exo*-adducts (20) and (23). Neither thermal nor hydrolytic (*e.g.* toluene-*p*-sulphonic acid–HOAc) treatment of these cycloadducts yielded the desired troponoids. Instead, expulsion of t-butyl acrylate yielded 3-hydroxypyridine by retro-1,3-dipolar cycloaddition.[13]

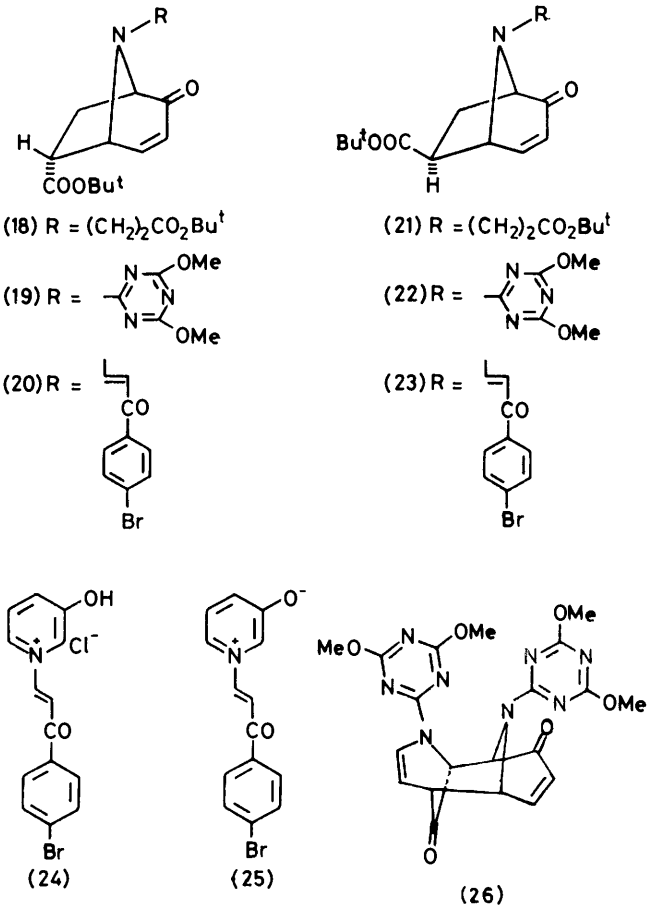


SCHEME 2

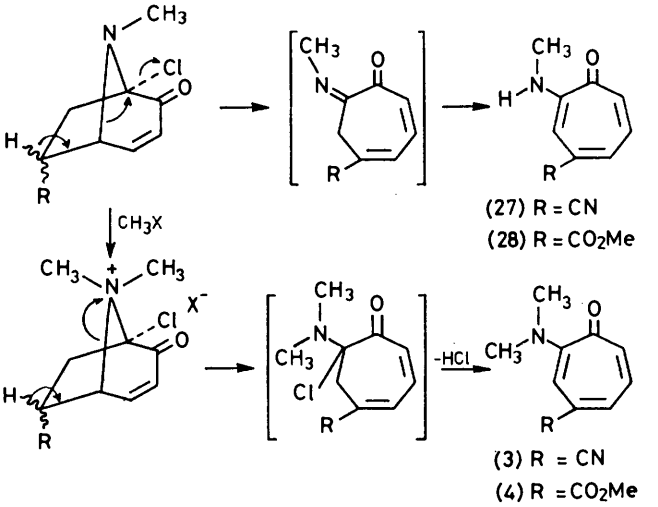
Activated Hofmann Displacement.—Incorporation of a good leaving group into the cycloadduct framework could enable Hofmann ring-opening of the tropane to the desired tropone without the usual quaternisation–basification sequence [11] (Scheme 3).

2-Chloro-3-hydroxypyridine, prepared following Schickh *et al.*,[19] was quantitatively quaternised by methyl toluene-*p*-sulphonate to the salt (29). The betaine (32), prepared *in situ*, reacted with the 2π addends acrylonitrile, methyl acrylate, and *N*-phenylmaleimide to yield the expected 2,6-adducts (35), (36), (39), (40), and (44) in moderate yields (*ca.* 50—80%). The heteroaromatic reactivity of 2-chloro-1-methyl-3-oxidopyridinium was comparable with that of 1-methyl-3-oxidopyridinium since both betaines are unreactive towards styrene.

2-Bromo-3-hydroxypyridine, prepared following Lewicka and Plazek,[20] was *N*-methylated by methyl toluene-*p*-sulphonate to give (30), m.p. 177—178 °C. The betaine (33), prepared *in situ*, reacted with the 2π addends acrylonitrile, *N*-phenylmaleimide, dimethyl maleate, and methyl acrylate to yield the corresponding expected adducts (37), (41), (45), (46), (42), and (47) in low yields (*ca.* 3—28%). In the case of methyl acrylate, the 7-*exo*-methoxycarbonyl isomer (47) was isolated and characterised. The only other example [21] in which

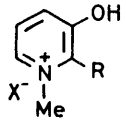


a 7-substituted cycloadduct [*i.e.* (49)] was isolated is the reaction of acrylonitrile with the 2,4-dinitrophenyl betaine (48). The heteroaromatic reactivity of 1-

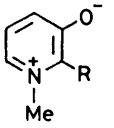


SCHEME 3

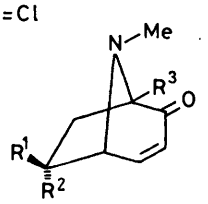
methyl-3-oxidopyridinium is considerably lowered by the 2-bromo-substitution.



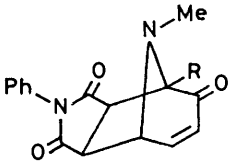
(29) R = Cl, X = OTs
(30) R = Br, X = OTs
(31) R = CN, X = Cl



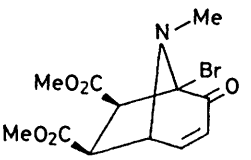
(32) R = Cl
(33) R = Br
(34) R = CN



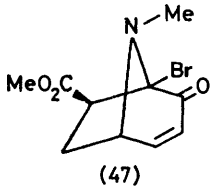
(35) R^1 = H, R^2 = CN, R^3 = Cl
(36) R^1 = H, R^2 = CO_2Me, R^3 = Cl
(37) R^1 = H, R^2 = CN, R^3 = Br
(38) R^1 = H, R^2 = CO_2Me, R^3 = CN
(39) R^1 = CN, R^2 = H, R^3 = Cl
(40) R^1 = CO_2Me, R^2 = H, R^3 = Cl
(41) R^1 = CN, R^2 = H, R^3 = Br
(42) R^1 = CO_2Me, R^2 = H, R^3 = Br
(43) R^1 = CO_2Me, R^2 = H, R^3 = CN



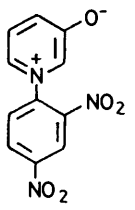
(44) R = Cl
(45) R = Br



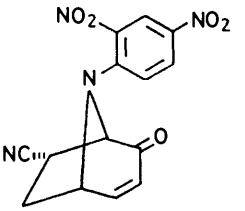
(46)



(47)



(48)



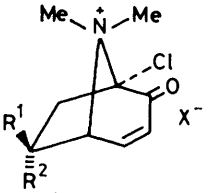
(49)

2-Cyano-3-hydroxy-1-methylpyridinium chloride (31) was prepared by the method of Clauson-Kaas *et al.*[22] Treatment of the salt with Et_3N yielded the stable yellow betaine (34), m.p. 215—217 °C. It reacted with methyl acrylate to yield a mixture of cycloadducts (38) and (43) in low yield (26%). The betaine (34) was unreactive towards numerous other 2π addends including acrylonitrile, 2-chloroacrylonitrile, styrene, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate.

The i.r. spectra of all the 2,6-adducts exhibited the characteristic αβ-unsaturated carbonyl stretching frequency. The n.m.r. spectra of the cycloadducts are shown in the Table.

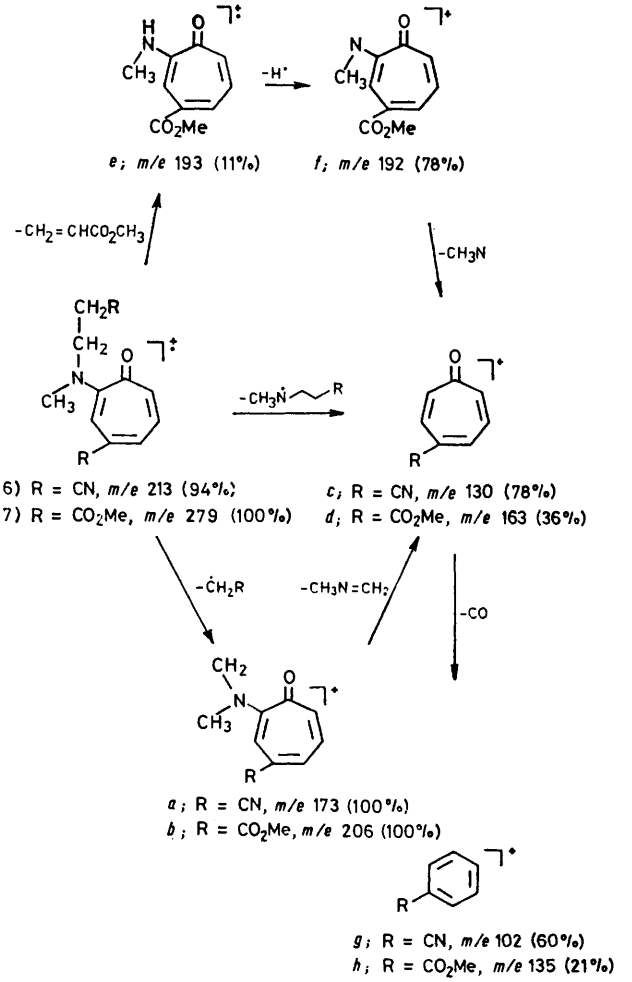
Base treatment of the chloro-cycloadducts (35) and (39) and (36) and (40) failed to produce the expected tropones (27) and (28) by proton abstraction followed by ring opening and chloride anion displacement (Scheme 3).

The cycloadducts (35) and (39) and (36) and (40) were readily quaternised using methyl toluene-*p*-sulphonate. The corresponding salts (50) and (51) and (52) and (53) proved difficult to separate and were treated with base to yield the expected dimethylaminotropones (3) and (4) in 10% yields.



(50) R^1 = H, R^2 = CN
(51) R^1 = CN, R^2 = H
(52) R^1 = H, R^2 = CO_2Me
(53) R^1 = CO_2Me, R^2 = H

Mass Spectrometry of Tropones.—The 2-dialkylaminotropones (6) and (7) principally fragment by loss of $\dot{C}H_2R$ to the ions *a* and *b*, respectively (Scheme 4). Further loss of $CH_3N{=}CH_2$ yields the ions *c* and *d*, respectively. Loss of the dialkylaminyl radical $CH_3\dot{N}$-



SCHEME 4

TABLE

^{1}H N.m.r. spectra of cycloadducts [a]

Proton	(6) [b]	(7) [b]	(12) [b]	(13) [b]	(14) and (15) [c]	(16) and (17) [c]	(18) and (21) [b]	(19) [b]	(20) [b,d]	(22) [b]	(23) [b,d]	(35) and (39) [b]	(36) and (40) [b]	(37) and (41) [b]	(38) and (43) [b]	(42) and (47) [b]	(47) [b]	(44) [b]	(45) [b]	(46) [b]
1			3.75 *e*	3.85 *e*	5.00 *e*	4.70 *e*	3.60 *f*	4.95 *e*	4.32 *e*	5.10 *e*	4.41 *e*									
3	6.35		6.05 *h*	6.20 *h*	6.80 *h*	6.60 *h*	6.00 *h*	5.85 *h*	5.98 *h*	5.85 *h*	5.98 *h*	6.20 *e*	6.00 *e*	6.27 *e* 6.18 *e*	6.08 *h*	6.10 *h*	6.10 *e*	6.10 *e*	6.15 *e*	6.13 *e*
4			6.65 *e*	6.80 *e*	7.80 *h*	7.50 *h*	7.00 *h*	7.20 *h*	7.18 *h*	7.20 *h*	7.24 *h*	7.00 *h*	7.00 *h*	7.06 *h*	7.00 *h* 6.88 *h*	7.00 *h*	6.95 *h*	7.30 *i*	7.04 *h*	7.04 *h*
5	6.85 *f*	6.90 *f*			5.80 *k*	5.40 *k*	4.00 *i*	5.35 *k*	4.66 *k*	5.40 *e*	4.75 *e*	4.00 *i*	3.90 *e* 4.00 *k*	4.75 *f*	4.20 *e* 4.08 *f*	4.00 *h*	4.00 *h*	4.30 *e*	4.28 *e*	4.48 *e*
6	6.85 *f*	6.90 *f*																		
6-*endo*				2.75 *f*	4.70 *f*	4.40 *f*	2.60 *i*			2.70 *i*	3.50 *h*	3.00 *i*	2.60 *i*	3.42 *f*	3.55 *e*	3.20 *f*	2.00 *h*	3.45 *e*	3.37 *i*	3.57 *e,i*
6-*exo*			2.75 *f*		4.70 *f*	4.40 *f*	2.60 *i*	3.35 *f*	2.98 *f*			3.00 *i*	2.60 *i*	3.42 *f*	3.25 *e*	3.20 *f*	2.70 *h*			
7	6.85	6.90																		
7-*endo*			1.80 *h*	2.10 *h*	4.70 *f*	4.40 *f*	2.60 *i*	2.00 *h*	2.13 *h*	2.85 *h*	2.06 *h*	3.00 *i*	2.60 *i*	2.15 *f*	2.35 *f*	2.10 *f*	3.20 *h*	2.35 *e*	3.37 *i*	3.09 *e*
7-*exo*			2.75 *f*	2.75 *f*	4.70 *f*	4.40 *f*	2.60 *i*	2.50 *f*	2.70 *f*	2.50 *i*	2.84 *f*	3.00 *i*	2.60 *i*	2.65 *f*	2.95 *i*	2.60 *f*				
N-Me					3.65 *g*	3.60 *g*						2.40 *g*	2.35 *g* 2.40 *g*	2.54 *g*	2.48 *g*	3.65 *g* 3.75 *g*	3.75 *g*	2.40 *g*	2.47 *g*	2.52 *g*
O-Me		3.40 *g* 3.70 *g*				3.40 *g* 3.50 *g*		3.80 *g*		3.80 *g*			3.60 *g* 3.70 *f*		3.64 *g* 3.73 *g*	2.40 *g* 2.50 *g*	2.50 *g*			3.70 *g* 3.64 *g*
C-Me			1.55 *g*	1.65 *g*			1.50 *g*	1.30 *g*	1.45 *g*	1.30 *g*	1.45 *g*									
N–CH_2-	3.70 *k*	3.60 *k*	2.75 *k*	2.75 *k*	4.30 *k*	3.80 *k*	2.60													
CH_2X	2.80 *k*	2.50 *k*			3.30 *k*	3.80 *k*														
Phenyl									7.69 *e* 7.48 *e*		7.40 *e* 7.50 *e*							7.30 *f*	7.34 *f*	

[a] Me_4Si as internal reference. [b] In $CDCl_3$. [c] In $(CD_3)_2CO$. [d] H-1′ and H-2′ doublets at δ 5.87 and *J* 14 Hz. *e* Doublet. *f* Double triplet. *g* Singlet. *h* Double doublet. *i* Overlapped with other signals. *j* Multiplet. *k* Triplet.

$(CH_2)_2R$, will also yield the troponium ions, *c* and *d*. Reverse thermal Michael addition of methyl acrylate to *e*, followed by loss of Ḣ to *f* and hence to *d* is also visualised. Expulsion of CO from *c* and *d* yield *g* and *h*, respectively. These fragmentations are consistent with those described [23] for other 2-alkylaminotropones.

EXPERIMENTAL

M.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer model 257 grating spectrophotometer, a Unicam SP800A spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100 n.m.r. spectrometer. Compounds were purified until they were observed as single spots on t.l.c. (Kieselgel PF 254).

One-pot Conversion of 3-*Hydroxypyridine into* 4-*Cyano-and* 4-*Methoxycarbonyl-tropolone* (1) *and* (2).—3-Hydroxypyridine (2.5 g, 0.025 mol), methyl acrylate (or acrylonitrile) (20 ml), and hydroquinone (50 mg) were refluxed for 15 h and evaporated to dryness at 15 mmHg. The yellow gum, $CHCl_3$ (30 ml), toluene (60 ml), and methyl fluorosulphonate (5 ml, 0.04 mol) were refluxed for 3 h, cooled, and decanted. The gum was washed with ether (2 × 50 ml), dried, and dissolved in distilled water (100 ml). Sodium hydrogen carbonate (5 g, 0.06 mol) was added and the mixture stirred at 20 °C for 90 min, acidified with concentrated HCl, and evaporated to dryness at 15 mmHg. 10% HCl (50 ml) was added and the whole heated at 100 °C for 1 h. The reaction was monitored by t.l.c. [EtOAc-light petroleum (40—60 °C) 1 : 1]. The tropolone (2) or (1) formed is stationary at the base line in this eluant. The acid solution was extracted with ether (4 × 50 ml), the extracts were dried ($MgSO_4$) and evaporated to yield the desired tropolone (2) or (1) (*ca.* 1 g, 25%) as yellow needles from Pr^iOH, m.p. 117—118 °C (lit.,[11] 116—118 °C) or m.p. 193—195 °C (lit.,[11] 194—195 °C), respectively.

8-(2-*Cyanoethyl*)-5-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6-endo- *and* 6-exo-*carbonitriles* (12) *and* (13).—A suspension of 3-hydroxy-6-methylpyridine (5 g, 0.05 mol) in excess of acrylonitrile (50 ml) was heated under reflux for 4 days. The mixture was evaporated to dryness and the residue chromatographed over alumina (B.D.H. Al_2O_3; neutral; CH_2Cl_2). A mixture of the *endo*- and *exo*-isomers (12) and (13) was obtained as yellow prisms (10 g, 90%), m.p. 128—129 °C (EtOH) (Found: C, 66.9; H. 6.1; N, 19.4 Calc. for $C_{12}H_{13}N_3O$: C, 66.9; H, 6.1; N, 19.5%); $\nu_{max.}$ ($CHBr_3$) 2 220 (CN) and 1 690 cm^{-1} (αβ-unsaturated ketone, C=O); $\lambda_{max.}$ ($CHCl_3$) 260 nm (log ε 2.70); *m/e* 215 ($M^{+\cdot}$, 30%), 162 ($M^{+\cdot} - C_3H_3N$), and 109 ($M^{+\cdot} - 2 \times C_3H_3N$).

6-endo- *and* 6-exo-*Cyano*-8-(2-*cyanoethyl*)-8-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene Perchlorates* (14) *and* (15).—A mixture of cycloadducts (8) and (9) [13] (5.0 g, 0.024 mol) in MeCN (100 ml) was treated with $AgClO_4$–4MeCN [14] (9.0 g, 0.024 mol) and MeI (50 ml) for 7 days at room temperature. The precipitate was filtered off, washed with MeCN (10 ml), and discarded. The combined filtrates were evaporated *in vacuo* to yield a yellow gum. The gum was triturated with $CHCl_3$ to realise the perchlorates (14) and (15) (6.4 g, 85%) as prisms (EtOH), m.p. 265—270 °C (Found: C, 45.5; H, 4.7; N, 13.2. Calc. for $C_{12}H_{14}ClN_3O_5$: C, 45.7; H, 4.4; N, 13.3%); $\nu_{max.}$ ($CHBr_3$) 2 220 (C≡N), 1 700 (αβ-unsaturated ketone, C=O), and 1 090 cm^{-1} (ClO_4); *m/e* 205 ($M^{+\cdot} - MeClO_4$, 10%).

6-exo- *and* 6-endo-*Methoxycarbonyl*-8-(2-*methoxycarbonylethyl*)-8-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene Perchlorates* (16) *and* (17).—The cycloadducts (10) and (11) (8.0 g, 0.03 mol) [13] in MeCN (100 ml) were treated with $AgClO_4$–4MeCN (11.0 g, 0.03 mol) and MeI (50 ml) at room temperature for 7 days as described above for (14) and (15). The title compounds (16) and (17) (7.0 g, 61%) were isolated as prisms (EtOH), m.p. 195—200 °C (Found: C, 43.7; H, 5.0; N, 4.1. Calc. for $C_{14}H_{20}ClNO_9$: C, 44.1; H, 5.3; N, 3.7%); $\nu_{max.}$ ($CHBr_3$) 1 730 (ester, C=O), 1 680 (αβ-unsaturated ketone, C=O), and 1 090 cm^{-1} (ClO_4^-); *m/e* 237 ($M^{+\cdot} - MeClO_4$, 20%).

2-[*Methyl*-(2-*cyanoethyl*)*amino*]-4-*cyanotropone* (6).—The perchlorate salts (14) and (15) (1 g, 0.003 mol) in water (25 ml) were stirred with 10% $NaHCO_3$ at room temperature for 20 min. The dark yellow solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated *in vacuo* to give the *title compound* (6) (0.55 g, 63%) as yellow needles, m.p. 110—112 °C (EtOH) (Found: C, 67.7; H, 5.5; N, 19.3. $C_{12}H_{11}N_3O$ requires C, 67.6; H, 5.2; N, 19.7%); $\nu_{max.}$ ($CHBr_3$) 1 620 (C=C), 1 580 (C=O), 1 220, and 1 210 cm^{-1} (C≡N); $\lambda_{max.}$ (EtOH) 432 (log ε 3.75), 352 (3.86), 280 (4.00), 265 (4.08), and 210 nm (3.98); *m/e* 213 (94%).

The aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$. The dried extracts afforded 4-cyanotropolone (1) (0.03 g, 10%) as yellow needles, 195—196 °C (lit.,[11] 194—195 °C) (EtOH).

4-*Methoxycarbonyl*-2-[*methyl*-(2-*methoxycarbonylethyl*)-*amino*]*tropone* (7).—The perchlorates (16) and (17) (2.0 g, 0.005 mol) in water (25 ml) were stirred at room temperature with 10% $NaHCO_3$ for 20 min. The dark yellow solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated to dryness to give a yellow residue from which the *title compound* (7) (0.8 g, 57%) was isolated by preparative t.l.c. (light petroleum–EtOAc, 4 : 1) as yellow needles, m.p. 50—51 °C (Found: C, 60.2; H, 6.2; N, 4.9. $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.1; N, 5.0%); $\nu_{max.}$ ($CHBr_3$) 1 730 (ester, C=O), 1 615 (C=C), and 1 570 cm^{-1} (C=O); $\lambda_{max.}$ (EtOH) 445 (log ε 3.71), 352 (3.81), 284 (3.97), 265 (4.00), and 210 nm (4.00); *m/e* 278 (100%).

The aqueous layer was acidified (10% HCl) and extracted with $CHCl_3$. The dried extracts yielded the 4-methoxycarbonyltropolone (2) (0.04 g, 12%) as yellow needles, m.p. 114—115 °C (lit.,[11] m.p. 116—118 °C) (EtOH).

t-Butyl 8-(2-*t-Butoxycarbonylethyl*)-2-*oxo*-8-*azabicyclo*-[3.2.1]*oct*-3-*ene*-6-endo- *and* -6-exo-*carboxylates* (18) *and* (21).—A solution of 3-hydroxypyridine (5 g, 0.06 mol), t-butyl acrylate (10 ml, 0.01 mol), and hydroquinone (0.2 g) in THF was heated under reflux for 3 days. The mixture was evaporated to dryness and the residue chromatographed on alumina (B.D.H.; neutral; CH_2Cl_2). A mixture of *endo*- and *exo*-adducts (18) and (21) was isolated as a yellow gum (8 g, 50%) which resisted all attempts for recrystallisation, $\nu_{max.}$ ($CHBr_3$) 1 740 (ester, C=O) and 1 690 cm^{-1} (αβ-unsaturated ketone, C=O); *m/e* 351 ($M^{+\cdot}$, 20%) and 95 ($M^{+\cdot} - 2 \times C_7H_{12}O_2$).

t-Butyl 8-(4,6-*Dimethoxy*-s-*triazin*-2-*yl*)-2-*oxo*-8-*azabicyclo*-[3.2.1]*oct*-3-*ene*-6-endo- *and* -6-exo-*carboxylates* (19) *and* (22).—The dimer (26) (0.5 g, 0.001 mol), t-butyl acrylate (10 g, 0.078 mol), and hydroquinone (0.1 g) were heated under reflux for 5 days. The mixture was evaporated to dryness and the residue purified by preparative t.l.c. [EtOAc–light petroleum (40—60 °C), 1 : 3]. The endo-*cycloadduct* (19) (40 mg, 6%) was isolated as prisms, m.p. 110—112 °C (EtOH) (Found: C, 56.7; H, 6.3; N, 15.0. $C_{17}H_{17}N_4O_5$ requires C, 56.4; H, 6.1; N, 15.5%); $\nu_{max.}$ ($CHBr_3$) 1 735 (ester, C=O), 1 680 (αβ-unsaturated ketone, C=O), 1 580, and 1 530 cm^{-1} (C=N); $\lambda_{max.}$ ($CHCl_3$) 247 nm (log ε 3.63); *m/e* 362 ($M^{+\cdot}$, 30%) and 234 ($M^{+\cdot} - C_7H_{12}O_2$). The exo-*isomer* (22) (100 mg, 14%) was isolated as prisms, m.p. 120—121 °C (EtOH–H_2O) (Found: C, 56.4; H, 5.9%); $\nu_{max.}$ ($CHBr_3$) 1 730 (ester, C=O), 1 680 (αβ-unsaturated ketone, C=O), 1 580, and 1 530 cm^{-1} (C=N); $\lambda_{max.}$ ($CHCl_3$) 247 nm (log ε 3.50); *m/e* 362 ($M^{+\cdot}$, 25%) and 234 ($M^{+\cdot} - C_7H_{12}O_2$, 100%).

t-Butyl 8-(4-*Bromobenzoylvinyl*)-2-*oxo*-8-*azabicyclo*[3.2.1]-*oct*-3-*ene*-6-endo- *and* -6-exo-*carboxylates* (20) and (23).—A solution of the betaine (25) (0.5 g, 0.001 6 mol) and t-butyl acrylate (3 ml) in MeCN (20 ml) was heated under reflux for 3 days. The reaction was monitored by t.l.c. [EtOAc–light petroleum (40—60 °C) 1 : 1]. The mixture was concentrated *in vacuo* and the pure isomers were separated by preparative t.l.c. [EtOAc–light petroleum (40—60 °C), 1 : 1]. The endo-*isomer* (20) (0.11 g, 22%) was isolated as pink prisms, m.p. 190—191 °C (Et_2O) (Found: C, 58.6; H, 5.3; Br, 18.3; N, 3.1. $C_{21}H_{22}BrNO_4$ requires C, 58.4; H, 5.1; Br, 18.5; N, 3.2%); $\nu_{max.}$ (Nujol) 1 730 (ester, C=O) and 1 690 cm^{-1} (αβ-unsaturated ester); $\lambda_{max.}$ ($CHCl_3$) 265 (log ε 4.27) and 334 nm (4.43); *m/e* 432 ($M^{+\cdot}$ 11%). The exo-*isomer* (23) (115 mg, 23%) was isolated as pink prisms, m.p. 165—166 °C (Et_2O) (Found: C, 58.6; H, 5.3; Br, 18.6; N, 3.2%); $\nu_{max.}$ (Nujol) 1 720 (ester, C=O) and 1 690 cm^{-1} (unsaturated ester, C=O); $\lambda_{max.}$ ($CHCl_3$) 265 (log ε 4.23) and 334 nm (4.41); *m/e* 432 ($M^{+\cdot}$, 8%).

2-*Chloro*-3-*hydroxy*-1-*methylpyridinium Toluene*-p-*sulphonate* (29).—2-Chloro-3-hydroxypyridine (1 g, 0.007 mol) and methyl toluene-*p*-sulphonate (2 g, 0.014 mol) were heated at 100 °C for 20 min. The cooled mixture was extracted with hot EtOAc to remove unreacted methyl toluene-*p*-sulphonate. The *title compound* (29) (2 g, 91%) was obtained as needles, m.p. 149—150 °C (EtOAc–MeCN) (Found: C, 49.2; H, 4.5; N, 4.6. $C_{13}H_{14}ClNO_3S$ requires C, 49.5; H, 4.4; N, 4.4%); $\nu_{max.}$ (Nujol) 2 500 (OH) and 1 570 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 225 (log ε 4.54), 265 (3.88), and 345 nm (3.88); *m/e* 143 ($M^{+\cdot} - HSO_3C_6H_4CH_3$, 20%); δ[$(CD_3)_2SO$] 2.00 (3 H, s, CCH_3), 3.90 (3 H, s, $\overset{+}{N}CH_3$), 6.90 (2 H, d, 3′-,5′-H), 7.35 (2 H, d, 2′-,6′-H, $J_{2',3'}$ 8 Hz), 7.40 (2 H, m, 4-,5-H), and 8.00 (1 H, dd, 6-H, $J_{4,6}$ 2, $J_{5,6}$ 8.0 Hz).

1-*Chloro*-8-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6-endo- *and* -6-exo-*carbonitriles* (35) and (39).—Et_3N (5 g, 0.05 mol) was added dropwise to a suspension of the salt (29) (0.5 g, 0.001 mol) and acrylonitrile (10 ml) in MeCN (25 ml). The mixture was heated under reflux for 1 h, cooled, and evaporated to dryness. The residue on dilution with water (5 ml) yielded the cycloadducts (35) and (39) (0.1 g, 50%) as yellow prisms, m.p. 125 °C (Found: N, 13.8. Calc. for $C_9H_9ClN_2O$: N, 14.2%); $\nu_{max.}$ ($CHBr_3$) 2 900 (CH), 2 220 (CN), and 1 700 cm^{-1} (αβ-unsaturated ketone, C=O); $\lambda_{max.}$ ($CHCl_3$) 200 nm (log ε 3.02); *m/e* 196.039 6 ($M^{+\cdot}$; calc. 196.636 8; 90%).

Methyl 1-*Chloro*-8-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6-endo- *and* -6-exo-*carboxylates* (36) *and* (40).—A suspension of the toluene-*p*-sulphonate (29) (0.5 g, 0.001 mol) and methyl acrylate (10 g, 0.12 mol) in MeCN (25 ml) were heated to reflux. Et_3N (5 g, 0.05 mol) was added dropwise and the mixture heated under reflux for 2 h. The reaction mixture was evaporated to dryness and the residue extracted with $CHCl_3$. The mixture of 6-*endo*- and 6-*exo*-isomers (36) and (40) was obtained as yellow needles. m.p. 85—86 °C (Pr^iOH) (0.2 g, 60%) (Found: C, 51.9; H, 5.3; N, 6.0. Calc. for $C_{10}H_{12}ClNO_3$: C, 52.3; H, 5.3; N, 6.1%); $\nu_{max.}$ ($CHBr_3$) 1 740 (ester, C=O) and 1 700 cm^{-1} (αβ-unsaturated ketone, C=O); $\lambda_{max.}$ ($CHCl_3$) 267 nm (log ε 4.74); *m/e* 230 ($M^{+\cdot}$, 80%) and 144 ($M^{+\cdot} - C_4H_6O$, 100).

1-*Chloro*-8-*methyl*-2-*oxo*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6,7-exo-N-*phenyldicarboximide* (44).—Et_3N (5 g, 0.05 mol) was added dropwise to a suspension of the toluene-*p*-sulphonate (29) (0.5 g, 0.001 mol) and *N*-phenylmaleimide (0.2 g, 0.001 mol) in MeCN (25 ml) and the mixture left at room temperature for 1 week. The mixture was evaporated to dryness and the residue on dilution with water (5 ml) yielded the *cycloadduct* (44) (0.25 g, 75%) as brown prisms, m.p. 99—100 °C (H_2O) (Found: H, 4.5; N, 9.2. $C_{16}H_{13}ClN_2O_3$ requires H, 4.1; N, 8.8%); $\nu_{max.}$ ($CHBr_3$) 1 720 cm^{-1} (C=O); *m/e* 316.062 4 ($M^{+\cdot}$; calc. 316.865 6; 10%) and 144 ($M^{+\cdot} - C_{10}H_7NO_2$, 25).

4-*Cyano*-2-*dimethylaminotropone* (3).—1-Chloro-8-methyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitriles (35) and (39) (2.1 g, 0.01 mol) were treated with methyl toluene-*p*-sulphonate at 80—85 °C for 3 h. The cold mixture was stirred with aqueous $NaHCO_3$ (2 g, 0.02 mol; 25 ml H_2O)

for 12 h. Extraction with $CHCl_3$ followed by preparative t.l.c. [EtOAc–light petroleum (40—60 °C), 1 : 2] yielded the tropone (3) (0.03 g, 10%) as yellow needles, m.p. 70—71 °C (lit.,[11] 72—73 °C) (EtOH).

2-Dimethylamino-4-methoxycarbonyltropone (4).—Methyl 1-chloro-8-methyl-2-oxo-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylates (36) and (40) (2.3 g, 0.01 mol) were treated with methyl toluene-*p*-sulphonate at 80—85 °C for 3 h. The cooled solution was treated with aqueous $NaHCO_3$ (2 g, 0.02 mol; 25 ml H_2O) for 12 h. Extraction with $CHCl_3$ followed by preparative t.l.c. yielded the tropone (4) (0.06 g, 10%) as yellow needles, m.p. 66—67 °C (lit.,[11] 66—67 °C) [light petroleum (40—60 °C)].

4-Methoxycarbonyl- (2) *and 4-Cyano-tropolone* (1).—A stirred solution of tropones (6) or (7) (2 g, 0.01 mol) in 10% aqueous HCl (50 ml) was heated at 60 °C for 1 h. The solution was left to cool to room temperature, extracted with Et_2O (3 × 50 ml), dried ($MgSO_4$), and evaporated to dryness to yield tropolones (2) and (1) (0.4 g, 25%) as yellow needles, m.p. 117—118 and 194 °C (Pr^iOH), respectively.

2-Bromo-3-hydroxypyridine.—A solution of bromine (9 ml) in 10% aqueous NaOH (150 ml) was added to a well stirred solution of 3-hydroxypyridine (15 g, 0.16 mol) in 10% aqueous NaOH (150 ml). After 20 h, concentrated HCl was added dropwise until pH 3.0 was attained. The resulting precipitate was filtered off, washed with water, and dried at 60 °C. Crystallisation from water yielded 2-bromo-3-hydroxypyridine (13.3 g, 48%) as needles, sublimes 161—163 °C (lit.,[20] m.p. 185—186 °C) (Found: C, 34.7; H, 2.6; N, 7.8. Calc. for C_5H_4BrNO: C, 34.5; H, 2.3; N, 8.1%); $\nu_{max.}$ (Nujol) 1 585, 1 310, and 682 cm^{-1} (CBr); δ[$(CD_3)_2SO$] 7.86 (1 H, t) and 7.29 (2 H, d).

2-Bromo-3-hydroxy-1-methylpyridinium Toluene-p-sulphonate (30).—2-Bromo-3-hydroxypyridine (0.5 g, 0.003 mol) and methyl toluene-*p*-sulphonate (1.0 g, 0.005 mol) were fused together at 80 °C on an oil-bath, for 45 min. On cooling, the *toluene-p-sulphonate* (30) was obtained as hexagonal plates (1.0 g, 97%), m.p. 177—178 °C (MeCN) (Found: C, 43.7; H, 3.9; Br, 22.5; N, 3.6. $C_{13}H_{14}BrNO_4S$ requires C, 43.3; H, 3.9; Br, 22.2; N, 3.9%); $\nu_{max.}$ (Nujol) 1 590, 1 485 (C=C), 1 360, 1 000, and 686 cm^{-1} (CBr); $\lambda_{max.}$ (EtOH) 225 (log ε 3.84), 265 (3.51), 322 (3.79), and 347 nm (3.54); δ[$(CD_3)_2SO$] 8.7 (1 H, m), 7.9 (2 H, m), 7.33 (4 H, AB system), 4.33 (3 H, s), and 2.27 (3 H, s); *m/e* 172 and 174 (78%).

Methyl 1-Bromo-8-methyl-2-oxo-8-azabicyclo[3.2.1]*oct-3-ene*-6-exo- *and* -7-exo-*carboxylates* (42) and (47).—2-Bromo-3-hydroxy-1-methylpyridinium toluene-*p*-sulphonate (30) (1.5 g, 0.004 mol) was suspended in MeCN (30 ml) and Et_3N (0.5 g, 0.005 mol) added. The resulting solution of the betaine was heated to reflux and methyl acrylate (1.5 g, 0.02 mol) and hydroquinone (1% by weight) added. Refluxing was continued during 11 h. Excess of solvent and dipolarophile were removed under vacuum to yield a reddish brown oil. The oil was separated by preparative t.l.c. into its components (Kieselgel PF 254; n-pentane–EtOAc, 1 : 1), two bands. The lower band was extracted with $CHCl_3$ (5 × 50 ml) to yield a pale green oil (0.212 g, 18.5%), identified by ^1H n.m.r. as a mixture of cylcoadduct isomers in ratio 2 : 1. The upper band yielded the exo-*isomer* (47) as a pale yellow oil (0.108 g, 9.5%) on extraction with $CHCl_3$ (4 × 50 ml), which crystallised as yellow cuboids, m.p. 106—108 °C (Pr^iOH) (Found: C, 43.7; H, 4.6; N, 5.2. $C_{10}H_{12}BrNO_3$ requires C, 43.8; H, 4.4; N, 5.1%); $\nu_{max.}$ ($CHBr_3$) 1 745 (ester, C=O) and 1 708 cm^{-1} (α-bromo-αβ-unsaturated C=O); $\lambda_{max.}$ (EtOH) 228 nm; *m/e* 275 and 273 (22%).

1-Bromo-8-methyl-2-oxo-8-azabicyclo[3.2.1]*oct-3-ene*-6,7-exo-N-*phenyldicarboximide* (45).—The salt (30) (0.5 g, 0.001 4 mol) was suspended in dry MeCN (15 ml) and Et_3N (5 ml) added, and the resulting solution of the betaine heated to reflux. *N*-Phenylmaleimide (0.96 g, 0.006 mol) was added and reflux continued during 0.5 h. After removal of the solvent *in vacuo*, the *adduct* was separated from the unreacted *N*-phenylmaleimide by preparative t.l.c. (Kieselgel PF 254; n-pentane–EtOAc, 1 : 1). Extraction of the lower band (upper is *N*-phenylmaleimide) with $CHCl_3$ (6 × 25 ml) yielded the *adduct* (45) (0.108 g, 22%) as light brown microcrystals, m.p. 173.5—174.5 °C (Pr^iOH) (Found: C, 53.0; H, 3.8; N, 7.6. $C_{16}H_{13}BrN_2O_3$ requires (C, 53.2; H, 3.6; N, 7.8%); $\nu_{max.}$ (Nujol) 1 790, 1 725 (imide, C=O, five-membered ring), 1 608, and 1 508 cm^{-1} C=C); $\lambda_{max.}$ (EtOH) 224 nm (log ε 4.24); *m/e* 360 and 362 (27%).

1-Bromo-8-methyl-2-oxo-8-azabicyclo[3.2.1]*oct-3-ene*-6-endo *and* -6-exo-*carbonitriles* (37) and (41).—The salt (30) (1.5 g, 0.004 mol) was suspended in acrylonitrile (4.4 g, 0.08 mol) and Et_3N (0.6 g, 0.006 mol) added. The mixture was heated to 60 °C, in presence of hydroquinone (0.9 g), during 95 h. After cooling, excess of acrylonitrile was removed under vacuum to yield a brown oil. Et_3N·HCl was precipitated from this by addition of Me_2CO (5 ml) and the filtrate was applied to a preparative t.l.c. plate, and the mixture separated [Kieselgel PF 254; light petroleum (40—60 °C)–EtOAc, 3 : 2]. Extraction of the slowest moving band with $CHCl_3$ (4 × 30 ml) yielded the adducts (37) and (41) as an orange oil (0.034 g, 3.4%), which could not be induced to crystallise, $\nu_{max.}$ ($CHBr_3$) 2 258 (C≡N) and 1 710 cm^{-1} (αβ-unsaturated C=O); $\lambda_{max.}$ (EtOH) 227 nm; *m/e* 239.988 5 ($M^{+\cdot}$; calc. 239.942 4; 10%).

Dimethyl 1-Bromo-8-methyl-2-oxo-8-azabicyclo[3.2.1]*oct-3-ene*-6,7-exo-*dicarboxylate* (46).—The salt (30) (1 g, 0.003 mol) was suspended in dry MeCN (10 ml) and Et_3N (0.3 g, 0.003 mol) added. Dimethyl maleate (0.8 g, 0.006 mol) and hydroquinone (0.03 g, 0.002 7 mol) were added to the resulting pale yellow solution. The mixture was heated at 60 °C during 190 h. On cooling, the solvent was removed under vacuum, and the resulting brown oil dissolved in $CHCl_3$ (5 ml) and filtered. The filtrate (two components by t.l.c.) was separated by preparative t.l.c. [Kieselgel PF 254; light petroleum (40—60 °C)–EtOAc, 1 : 1]. Extraction of the band of lower R_F with $CHCl_3$ (4 × 50 ml) yielded the *adduct* (46) as a yellow oil (0.065 g, 7%); $\nu_{max.}$ 1 750 (ester C=O) and 1 705 cm^{-1} (αβ-unsaturated C=O); *m/e* 331.004 7 ($M^{+\cdot}$ calc. 331.006 6; 16%).

Methyl 1-Cyano-8-methyl-2-oxo-8-azabicyclo[3.2.1]*oct-3-ene*-6-endo- *and* -6-exo-*carboxylates* (38) *and* (43).—2-Cyano-3-hydroxy-1-methylpyridinium chloride (31) (0.5 g, 0.003 mol) and methyl acrylate (20 ml, 0.22 mol) were heated to reflux. Et_3N (1 ml, 0.007 mol) was added to the mixture, and reflux was continued during 72 h. On cooling, the excess of methyl acrylate was removed under vacuum to leave a brown gum. This was washed with dry Et_2O (150 ml) in several portions. The combined ether solutions were evaporated *in vacuo* to yield a 1 : 1 mixture of *endo*- and *exo*-cycloadducts (0.17 g, 26%) as pale yellow needles (Pr^iOH), m.p. 102.5—104 °C (Found: C, 60.2; H, 5.5; N, 12.8. Calc. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7%); $\nu_{max.}$ ($CHBr_3$) 2 260 (C≡N), 1 740 (ester C=O), 1 705 (αβ-

unsaturated ketone C=O), and 1 610 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 227 nm (log ε 4.0); *m/e* 220.

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