1,3-Dipolar Character of Six-membered Aromatic Rings. Part III.[1] 2-Methyl-3-oxidoisoquinolinium. A Novel Route to Benzotropones

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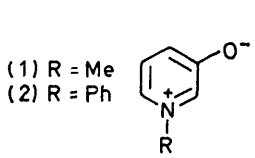
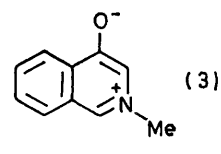
The title compound reacts as a 1,3-dipole across the 1- and 3-positions with acrylonitrile and methyl acrylate. The stereochemistry of the adducts is deduced from n.m.r. spectra. The methiodides of the adducts undergo base-catalysed elimination to form 2-aminobenzotropones.

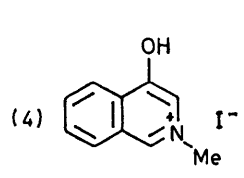
1,3-DIPOLAR cycloadditions have received intensive investigation for some years.[2,3] Most such reactions have involved open-chain dipoles; some cyclic dipoles have also been investigated,[4] including cyclic betaines with 1,3-dipolar character which have generally possessed five-membered rings.[5] Recently, certain six-membered aromatic betaines have been shown to react as 1,3-dipoles:[6] 1-methyl-3-oxidopyridinium (1) reacts with *N*-phenylmaleimide, acrylonitrile, methyl acrylate, and methyl methacrylate to give cycloadducts.[7] 1-Phenyl-3-oxidopyridinium (2) also possesses 1,3-dipolar reactivity.[8]





(3)

We have now examined the reactions of 2-methyl-4-oxidoisoquinolinium (3) as a 1,3-dipole. Mruk and Tieckelmann [9] described 1,4-cycloadditions of *N*-methyl-3-isoquinolone and Bradsher and Day [10] demonstrated that *N*-methylisoquinolinium salts undergo 1,4-cycloaddition with ethyl vinyl ether. Recently Ames and Novitt [11] have shown that the N(1)–N–C(3) unit of the simple cinnoline ring in anhydro-4-hydroxy-2-methylcinnolinium hydroxide undergoes 1,3-dipolar cycloadditions. Ullman and Milks,[12a] and recently Lown and Matsumoto [12b] have found that benzopyrylium oxides also behave as 1,3-dipoles. No examples of 1,3-dipolar reactivity in the isoquinoline series have been reported.



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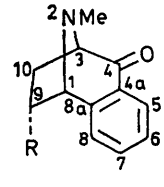


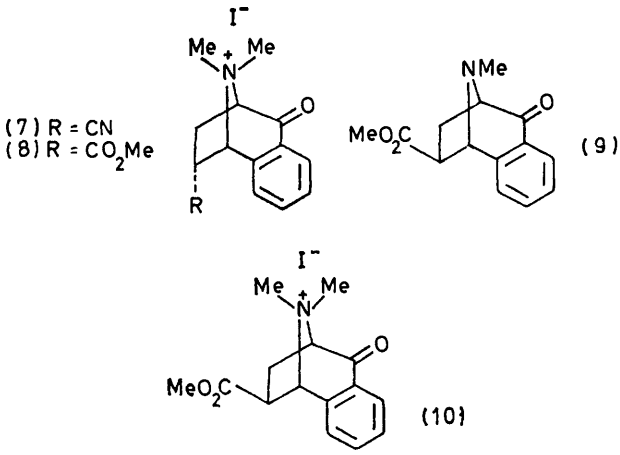
(5) R = CN
(6) R = CO_2Me

4-Hydroxy-2-methylisoquinolinium iodide (4) was ion-exchanged to give the betaine (3) as a red syrup, which crystallised from ethanol as a solid hydrate, m.p. 53—54°.† Compound (3) with acrylonitrile gave an adduct (5) readily soluble in organic solvents but

† It is not necessary to isolate compound (3) as the solid hydrate; the syrup shows the same 1,3-dipolar reactivity.

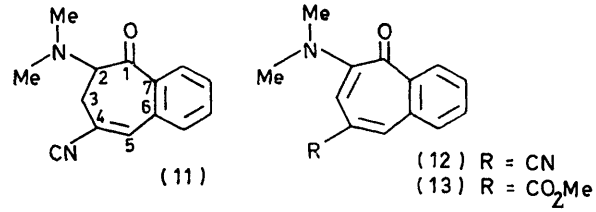
[1] Part II, see ref. 15.
[2] L. I. Smith, *Chem. Rev.*, 1938, **23**, 193.
[3] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565
[4] W. Baker and W. D. Ollis, *Quart. Rev.*, 1957, **11**, 15.
[5] P. Rajagopalan and P. Penev, *Chem. Comm.*, 1971, 490.
[6] S. Oida and E. Ohki, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 2461.
[7] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (*C*), 1971, 874.
[8] Y. Takeuchi, N. Dennis, A. R. Katritzky, and I. Taulov, 3rd International Congress of Heterocyclic Chemistry, Sendai, Japan, 1971.
[9] N. J. Mruk and H. Tieckelmann, *Tetrahedron Letters*, 1970, 1209.
[10] C. K. Bradsher and F. H. Day, *Tetrahedron Letters*, 1971, 409.
[11] D. E. Ames and B. Novitt, *J. Chem. Soc.* (*C*), 1969, 2355.
[12] (*a*) E. F. Ullman and J. E. Milks, *J. Amer. Chem. Soc.*, 1962, **84**, 1315; (*b*) J. W. Lown and K. Matsumoto, *Canad. J. Chem.*, 1971, **49**, 3443.

insoluble in water. Chromatography showed the presence of three components, one of which was obtained as pale yellow needles, m.p. 127—128°. The i.r. spectrum showed the presence of ν(C≡N) and ν(C=O), and the tricyclic structure (5) was demonstrated by the n.m.r. spectrum (Table 1). The signals for the bridgehead protons H-1 and H-3 appear as a doublet and a doublet of doublets respectively. The 6·9 Hz coupling between H-1 and H-9 established the *endo*-configuration of the cyano-group. Compound (5) readily forms the methiodide (7), the n.m.r. spectrum of which confirms the structural and stereochemical assignments for compound (5).



Reaction of the betaine (3) with methyl acrylate produced two cycloadducts. The i.r. spectrum of (9), m.p. 101—102°, included ν(C=O) (ester) and ν(C=O) (ketone). The n.m.r. (Table 1) signals for the bridgehead protons H-1 and H-3 appear as a singlet and a doublet of doublets: lack of appreciable coupling (<0·5 Hz) between H-1 and H-9 established the *exo*-configuration of the methoxycarbonyl group. A second cycloadduct (6) was isolated chromatographically from the betaine-methyl acrylate reaction as an oil. The i.r. spectrum included ν(C=O) (ester) and ν(C=O) (ketone), and the mass spectrum had *m/e* 245. As in the case of adduct (5), the signals for the bridgehead protons appear as a doublet and a doublet of doublets. The 6·4 Hz coupling between H-1 and H-9 (Table 1) established the *endo*-configuration of the methoxycarbonyl group. Adducts (6) and (9) both react with methyl iodide to produce the methiodides (8) and (10).

Much work has been directed towards the synthesis of tropones and tropolones.[13] Recently 2-aminotropones and the corresponding tropolones were synthesised from 8-azabicyclo[3,2,1]oct-3-en-2-one methiodides by Hofmann elimination.[14,15] Hofmann elimination applied to compound (7) leads to a benzocycloheptadienone. There are two possible sites for base attack, *i.e.* H-9 and H-10, but the former is activated by a strongly electron-withdrawing cyano-group and so ring opening should proceed solely *via* cleavage of the C(5)–N bond to give the benzocycloheptadienone (11). On treatment with silver oxide, the methiodide (7) gave



2-dimethylamino-4-cyano-6,7-benzotropone (12) as yellow needles, m.p. 126—127°. It had previously been shown [15] that Hofmann elimination of cycloadduct (14)

TABLE 1

Proton n.m.r. spectra of cycloadducts [a]

Chemical shifts (δ)	Compound (5) [b]	(9) [b]	(6) [b]	(7) [c]	(10) [c]
3	3·95	4·23	3·95	5·15	5·58
1	4·21	4·02	4·41	5·61	5·18
9-*exo*	3·59			4·78	
10-*endo*	2·07	2·09		2·39	
10-*exo*	2·92				
2-Me	2·40	2·43	2·38	3·38	3·27
				3·18	3·11
5	8·05	7·96		8·13	8·05
6	7·59	7·56		7·98	7·92
7	7·39	7·36		7·74	7·69
8	7·23	7·21		7·66	7·62
CO_2Me		3·75	3·42		3·78
Coupling constants (Hz)	**(5) [b]**	**(9) [b]**	**(6) [b]**	**(7) [c]**	**(10) [c]**
3,10-*endo*	0·8	1·0	1·0	1·2	0·8
3,10-*exo*	6·7	6·0	7·4	7·6	6·3
1,9-*endo*		0·0			0·0
1,9-*exo*	6·9		6·4	6·2	
9-*endo*, 10-*endo*		11·2			
9-*exo*, 10-*endo*	4·4			4·2	
9-*exo*, 10-*exo*	11·4			11·0	
10-*endo*, 10-*exo*	12·6	14·2			
5,6	7·5	7·4		7·4	7·4
5,7	1·6	1·6		1·4	1·8
6,7	7·2	7·4		7·4	7·4
6,8	1·5	1·6		1·4	1·6
7,8	7·2	7·4		7·4	7·4

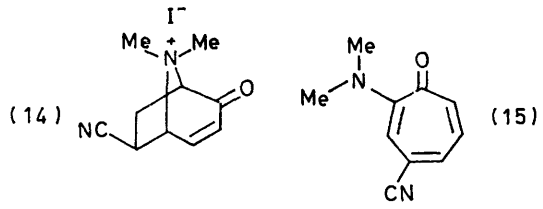
[a] δ In p.p.m. relative to Me_4Si as internal standard; coupling constant in Hz. [b] In $CDCl_3$. [c] In $(CD_3)_2SO$.

is followed by spontaneous aromatisation to the dimethylaminocyanotropone (15), and compound (11) evidently similarly undergoes aromatisation to yield (12). The benzotropone (12) unlike compound (15),[15] was stable to air and light. The structure was confirmed by the mass spectrum (*m/e* 224), the n.m.r. spectrum (Table 2, NMe_2 and the absence of aliphatic protons), and the i.r. spectrum [ν(C≡N) and ν(C=O)].

Treatment of the quaternary salt (8) with silver oxide also produced the corresponding tropone, 2-dimethylamino-4-methoxycarbonyl-6,7-benzotropone (13). The structure was confirmed by the n.m.r. spectrum (Table 2, NMe_2 and CO_2Me, and the absence of aliphatic protons) the i.r. spectrum and the molecular ion at *m/e* 257. Degradation of the isomeric methiodide (10)

[13] P. L. Pauson, *Chem. Rev.*, 1955, **55**, 9.
[14] A. R. Katritzky and Y. Takeuchi, *J. Amer. Chem. Soc.*, 1970, **92**, 4134.
[15] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (*C*), 1971, 878.

with silver oxide produced the same tropone (13) in good yield.



As in previous work,[15] dehydrogenation followed ring-opening. Since silver oxide can behave as an oxidising agent, sodium hydrogen carbonate was also used as the base for Hofmann elimination. In all three cases,

TABLE 2

Proton n.m.r. spectra of substituted benzotropones

Substituent		Chemical shift [a]				
2-	4-	H_3	H_5	NMe_2	Aromatic	CO_2Me
NMe_2	CN	5·94	7·28	3·00	8·04—7·84, 7·70—7·50	
NMe_2	CO_2Me	6·82	7·32	2·95	8·08—7·94, 7·64—7·50	3·91

[a] δ In p.p.m. from internal Me_4Si in $CDCl_3$.

the methiodides (7), (8), and (10) were again smoothly converted into the corresponding dimethylaminobenzotropones. Presumably, the mechanism involves donation of hydride from the enolate anion of (11) to a neutral species of (11) to produce the tropone (12) and a cycloheptenone derivative which was not isolated.

This synthetic sequence to 6,7-benzotropones is of preparative significance in view of the tedious methods previously used.[16]

EXPERIMENTAL

The m.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer model 257 grating spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100MHz n.m.r. spectrometer.

4-Hydroxy-2-methylisoquinolinium Iodide (4).—4-Hydroxyisoquinoline [17] (12·2 g, 0·084 mol), methyl iodide (150 ml), acetone (90 ml), and benzene (90 ml) were kept at 20° for 2 days. The *methiodide* (4) (15·2 g, 63%), crystallised from acetone–benzene (50 : 50) as plates, m.p. 144—145° (decomp.) (Found: C, 41·6; H, 3·4; N, 4·9. $C_{10}H_{10}INO$ requires C, 41·8; H, 3·5; N, 4·9%).

2-Methyl-4-oxidoisoquinolinium (3).— 4-Hydroxy-2-methylisoquinolinium iodide (17·2 g, 0·06 mol) in distilled water (200 ml) was passed through an Amberlite IRA-401 column (300 g) followed by water (*ca.* 2 l) until the eluate was neutral. The combined eluate was evaporated at 50°/10 mm to give the crude betaine as red syrup (8·3 g, 87%) which showed no further weight loss on heating at 60°/9 mm (this was used for the subsequent reactions). The syrup, which solidified when set aside in ethanol (10 ml) was cooled with solid carbon dioxide–acetone to give a yellow solid which after repeated recrystallisation from ethanol gave the *betaine monohydrate* as hygroscopic yellow needles, m.p. 53—54° [Found: C, 67·6; H, 6·2; N, 7·4. $C_{10}H_9NO(H_2O)$ requires C, 67·8; H, 6·3; N, 7·9%]; $\nu_{max.}$ (Nujol) 1590, 1605, and 1675 cm^{-1}.

Reactions of the Betaine (3).—(i) *With acrylonitrile.* Compound (3) (8·0 g, 0·045 mol) and acrylonitrile (50 ml) were heated under reflux in dry THF (125 ml) with hydroquinone (0·20 g). After 72 h almost all compound (3) had disappeared, and the solvent was evaporated at 35°/10 mm. The brown syrup (8·3 g) was chromatographed on silica gel (400 g, $CHCl_3$). The eluate was evaporated off and the residue (8·0 g) crystallised from ethyl acetate to afford pale yellow needles of *1,2,3,4-tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline*-9-endo-*carbonitrile* (5) (1·9 g, 18%), m.p. 127—128° (Found: C, 73·3; H, 5·6; N, 13·2. $C_{13}H_{12}N_2O$ requires C, 73·6; H, 5·7; N, 13·2%); $\nu_{max.}$ ($CHCl_3$) 1604 (C=C), 1690 (C=O), 2248 (C≡N), 2810 (*N*-methyl), and 2859 cm^{-1}; *m/e* 212.

(ii) *With methyl acrylate.* Compound (3) (7·75 g, 0·044 mol) and methyl acrylate (50 ml) were heated under reflux in dry THF (125 ml) with hydroquinone (0·20 g) for 50 h. Unreacted betaine was removed by decantation, and the solution was evaporated at 40°/10 mm. The residual brown syrup (8·0 g) was chromatographed on silica gel (400 g, $CHCl_3$). The eluate was evaporated off and the residue was kept at 0°; it gradually solidified. Repeated crystallisation from ethyl acetate–light petroleum gave pale green needles of *methyl 1,2,3,4-tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline*-9-exo-*carboxylate* (9) (1·5 g, 13%), m.p. 101—102° (Found: C, 68·4; H, 6·0; N, 5·7. $C_{14}H_{15}NO_3$ requires C, 68·6; H, 6·2; N, 5·7%); $\nu_{max.}$ ($CHCl_3$) 1223 (C–O), 1609 (C=C), 1696 (ketone, C=O), 1739 (ester, C=O), and 2823 (*N*-methyl) cm^{-1}; *m/e* 245.

The mother liquors were combined and chromatographed on silica gel (Kieselgel PF254, ethyl acetate). A second cycloadduct was isolated and purified by distillation (120°/0·2 mm). *Methyl 1,2,3,4-tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline*-9-endo-*carboxylate* (6) was obtained as a pale green viscous oil (1·2 g, 10%) (Found: C, 68·5; H, 6·2; N, 5·6. $C_{14}H_{15}NO_3$ requires C, 68·6; H, 6·2; N, 5·7%); $\nu_{max.}$ ($CHCl_3$) 1220 (C–O), 1605 (C=C), 1695 (ketone, C=O), 1740 (ester, C=O), and 2835 (*N*-methyl) cm^{-1}; *m/e* 245.

Quaternisation of 1,2,3,4-Tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline-9-endo-*carbonitrile* (5).—Compound (5) (0·10 g, 0·47 × 10^{-3} mol) in ethyl acetate (30 ml) and methyl iodide (10 ml) at 20° for 4 days gave the *quaternary salt* (7) (0·13 g, 78%) which crystallised from ethanol as pale yellow needles, m.p. 163—164° (decomp.) (Found: C, 47·7; H, 4·4; N, 7·8. $C_{14}H_{15}IN_2O$ requires C, 47·5; H, 4·3; N, 7·9%); $\nu_{max.}$ (Nujol) 1603 (C=C) and 1712 (ketone, C=O) cm^{-1}.

Quarternisation of Methyl 1,2,3,4-Tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline-9-endo-*carboxylate* (9).—Compound (9) (0·50 g, 0·0023 mol) in ethyl acetate (20 ml) and methyl iodide (10 ml) at 20° for 2 days gave the *methiodide* (10) (0·62 g, 79%), which crystallised from water as colourless plates, m.p. 185° (decomp.) (Found: C, 46·4; H, 4·9; N, 3·8. $C_{15}H_{18}INO_3$ requires C, 46·5; H, 4·7; N, 3·6%); $\nu_{max.}$ (Nujol) 1215 (C–O), 1607 (C=C), 1703 (ketone, C=O), and 1735 (ester, C=O) cm^{-1}.

Quarternisation of Methyl 1,2,3,4-Tetrahydro-2-methyl-4-oxo-1,3-ethanoisoquinoline-9-endo-*carboxylate* (6).—Compound (6) (0·65 g, 0·0027 mol) in ethyl acetate (20 ml) and methyl iodide (15 ml) at 20° for 2 days gave the

[16] T. Nozoe, 'Non-benzenoid Aromatic Hydrocarbons,' ed. D. Ginsburg, Interscience, New York, 1959, p. 339.

[17] E. Ochiai and M. Ikehara, *Chem. Pharm. Bull.* (*Japan*), 1955, **3**, 454.

quarternary salt (8) (0·91 g, 89%), which crystallised from ethanol as colourless plates, m.p. 169—170° (decomp.) (Found: C, 46·4; H, 4·7; N, 3·7. $C_{15}H_{18}INO_3$ requires C, 46·5; H, 4·7; N, 3·6%); $\nu_{max.}$ (Nujol) 1232 (C–O), 1603 (C=C), 1703 (ketone, C=O), and 1742 (ester, C=O) cm^{-1}.

Treatment of the Methiodide (7) *with Base.*—(a) *With silver oxide.* Compound (7) (1·0 g, $2·8 \times 10^{-3}$ mol) in distilled water (20 ml) and silver oxide (0·70 g) were stirred at 30° for 10 min and the filtrate was extracted with ether (50 ml). The dried extracts were evaporated to afford *2-dimethylamino-4-cyano-6,7-benzotropone* (12), which was chromatographed on silica gel (Kieselgel PF254, $CHCl_3$) and then crystallised from ethanol–water as golden yellow needles (0·50 g, 79%), m.p. 126—127° (Found: C, 74·7; H, 5·4; N, 12·6. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%); $\nu_{max.}$ ($CHCl_3$) 1562, 1594 (C=C), 1634 (C=O), 2229 (C≡N), and 2809 (*N*-methyl) cm^{-1}; *m/e* 224.

(b) *With sodium hydrogen carbonate.* Compound (7) (1·4 g, 0·0039 mol) and sodium hydrogen carbonate (1·6 g) in distilled water (100 ml) were stirred at 50°. The reaction was monitored by t.l.c.: the same amount of reaction mixture was removed at intervals with a capillary tube and applied to the plate (silica gel). Compound (12) ascended rapidly ($CHCl_3$, R_F 0·49) while the unchanged quarternary species remained at the origin. The reaction was stopped when the size of the yellow spot became constant (2 h). An ether extract gave compound (12) (0·30 g, 34%), which was purified as before by thick-layer chromatography (Kieselgel PF254) and crystallised from ethanol–water. No product was obtained by acidification of the aqueous layer.

Treatment of the Methiodide (10) *with Base.*—(a) *With silver oxide.* The methiodide (10) (1·0 g, 0·0025 mol) and silver oxide (0·70 g) were stirred at 20° for 10 min in distilled water (30 ml). The solid was filtered off and the filtrate was extracted with ether (150 ml). The dried extracts were evaporated to give *2-dimethylamino-4-methoxycarbonyl-6,7-benzotropone* (13), which was chromatographed on silica gel (Kieselgel PF254, $CHCl_3$) and then crystallised from ethanol–water to give golden yellow needles (0·20 g, 30%), m.p. 99—100° (Found: C, 70·1; H, 6·0; N, 5·4. $C_{15}H_{15}NO_3$ requires C, 70·0; H, 5·9; N, 5·4%); $\nu_{max.}$ ($CHCl_3$) 1230 (C–O), 1575, 1600 (C=C), 1633 (ketone, C=O), and 1715 (ester, C=O) cm^{-1}; *m/e* 257.

(b) *With sodium hydrogen carbonate.* Compound (10) (1·5 g, 0·0038 mol) and sodium hydrogen carbonate (1·5 g) in distilled water (100 ml) were stirred at 20°. The reaction was monitored by t.l.c. (silica gel, $CHCl_3$, R_F 0·63). After 4 h, the mixture was extracted with ether (2 × 50 ml): the extract yielded compound (13) (0·24 g, 24%). No residue was obtained after acidification of the aqueous layer.

Treatment of the Methiodide (8) *with Base.*—(a) *With silver oxide.* The methiodide (8) (0·60 g, 0·0016 mol) and silver oxide (0·70 g) were stirred at 50° for 15 min in distilled water (20 ml). The black solid was filtered off and the green filtrate was extracted with ether (200 ml). The dried extracts were evaporated to give *2-dimethylamino-4-methoxycarbonyl-6,7-benzotropone* (13), which was chromatographed on silica gel (Kieselgel PF254, $CHCl_3$) and then crystallised from ethanol–water to give golden yellow needles (0·10 g, 25%), m.p. 98—100°. No residue was obtained on acidification of the aqueous layer.

(b) *With sodium hydrogen carbonate.* Compound (8) (0·54 g, 0·0018 mol) and sodium hydrogen carbonate (1·5 g) in distilled water (100 ml) was stirred at 30° for 2 h. The green mixture was extracted with ether (2 × 50 ml): the extract yielded compound (13) (0·097 g, 27%). Again no residue was obtained after acidification of the aqueous layer.

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