1,3-Dipolar Cycloadditions of *anhydro*-5-Hydroxyoxazolium Hydroxide Generated from 2-Piperidinecarboxylic Acid. Isolation of the Primary Adduct and Synthesis of Tetrahydroindolizines (1)

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1,3-Dipolar cycloaddition reactions of *anhydro*-5-hydroxyoxazolium hydroxide **3** generated from 2-piperidinecarboxylic acid and acetic anhydride, with dimethyl and diethyl acetylenedicarboxylates, dibenzoylacetylene, *p*-benzoquinone, and 1,4-naphthoquinone gave the corresponding tetrahydroindolizines. In the case of the reaction with *p*-benzoquinone, the dihydroindolizine **12** was also formed. The primary *N*-bridged lactone intermediate **4** was isolated from the reaction of **2** with dibenzoylacetylene. Several attempted conversions of these tetrahydroindolizines into the corresponding aromatic indolizines were fruitless.

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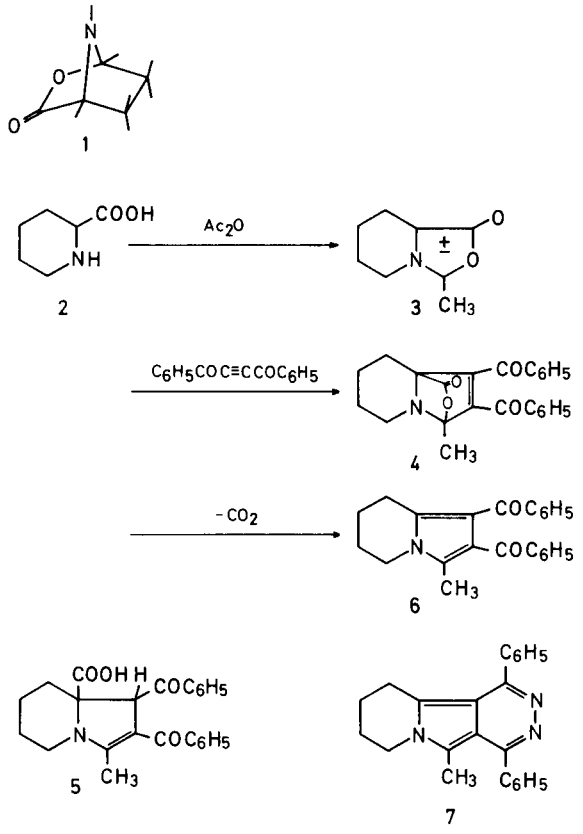
Mesoionic *anhydro*-5-hydroxyoxazolium hydroxides (2) have recently been employed in the facile synthesis of a variety of heterocycles such as pyrroles (3), pyrrolines (4), and precursors to the mitomycins (5). The generally accepted mechanism (3-6) of these reactions involves a 1,3-dipolar cycloaddition of the *anhydro*-5-hydroxyoxazolium hydroxide, behaving like a cyclic azomethine ylide, with a suitable dipolarophile, followed by evolution of carbon dioxide to give the product. However, no primary adduct of the type **1** has been isolated (6), although the bicyclic primary adducts have been isolated in the reactions of other related mesoionic systems (7). On the other hand, it is apparent that, when 2-piperidinecarboxylic acid (**2**) is employed as the precursor to **3** (5,8), its reaction with a dipolarophile provides a useful route to the indolizine framework (9). Thus, the authors report, in this note, a formation of the stable 1:1 adduct from the reaction of 2-piperidinecarboxylic acid (**2**) with dibenzoylacetylene in which the element of carbon dioxide is retained, and an application of this reaction in the synthesis of tetrahydroindolizines.

Scheme I



Reaction of **2** and dibenzoylacetylene in the presence of acetic anhydride at 70° for 72 hours produced, after successive purification by silica gel column chromatography (benzene/chloroform) and preparative thin layer chromatography (benzene/ether), the *N*-bridged lactone **4** in 10% yield. The ^{1}H nmr spectrum of **4** displayed four methylene protons at δ 1.7-2.2 (m, 6 and 7-H), three methyl protons at 2.13 (s), two methylene protons at 2.76 (t, 8-H), and two methylene protons at 4.34 (t, 5-H) together with ten aromatic protons as multiplet at 7.0-7.4, thus the structure of carboxylic acid **5** (6a) being ruled out; there was no absorption due to methine proton. Its structure was also supported by analytical and spectral (mass, ir and ^{13}C-nmr) data (see Experimental). In addition to **4** was obtained a 45% yield of 1,2-dibenzoyl-3-methyl-5,6,7,8-tetrahydroindolizine (**6**) (Table I). Thermal decomposition of **4** in refluxing xylene produced the pyrrole **6**, which, in turn, gave the tetrahydropyridazino-[4,5-*a*]indolizine **7** in 17% yield on treatment with hydrazine hydrate.

The analogous reactions of **2** with such dipolarophiles

Table I

5,6,7,8-Tetrahydroindolizines

Compound	Yield, %	M.p., °C	Ir (a) cm^{-1} ν C=O	Nmr (in chloroform-d) H-6,7 (b)	H-8 (c)	H-5 (c)	3-CH_3 (d)	R	M^+, m/e	Found, % C	H	N
6	45	106-108	1635	1.72-2.25	3.03	3.91	2.40	7.00-7.36 (e)	343	--------	---(f)	3.82
									$C_{23}H_{21}O_2N$	(80.44	6.16	4.08)
8	28	83-86	1713	1.67-2.11	2.97	3.70	2.31	3.78, 3.82 (g)	251	62.31	6.98	5.63
									$C_{13}H_{17}O_4N$	(62.14	6.82	5.57)
9	30	syrup	1690	1.65-2.10	2.98	3.76	2.32	1.31, 1.33 (h);	279	64.23	7.58	4.73
								4.26, 4.30 (i)	$C_{15}H_{21}O_4N$	(64.49	7.58	5.01)
10	19	183-185.5	1638	1.70-2.20	3.11	3.83	2.52	6.52 (j)	215	72.29	6.01	6.40
									$C_{13}H_{13}O_2N$	(72.54	6.09	6.51)
11	43	172-174	1660	1.60-2.10	3.21	3.73	2.50	7.56-7.71,	265	76.97	5.68	5.41
								8.07-8.29 (k)	$C_{17}H_{15}O_2N$	(76.96	5.70	5.28)
13	70	159-163	1630	1.70-2.20	2.98	4.02	7.01 (1)	7.0-7.6 (m)	329	80.09	5.88	4.28
									$C_{22}H_{19}O_2N$	(80.22	5.81	4.25)
14	5	174-178	1640	1.70-2.30	3.11	4.02	7.11 (1)	6.61 (n)	201	71.36	5.30	6.70
			1664						$C_{12}H_{11}O_2N$	(71.62	5.51	6.96)
15	34	211-212.5	1640	1.75-2.20	3.18	4.03	7.20 (1)	7.60-7.80,	251	76.19	5.09	5.44
			1660					8.10-8.33 (o)	$C_{16}H_{13}O_2N$	(76.47	5.22	5.57)

(a) Potassium bromide disk. (b) Multiplet, 4H. (c) Triplet (J = 6 Hz), 2H. (d) Singlet, 3H. (e) Multiplet, 10H, aromatic. (f) Not purified by recrystallization from any solvents. (g) Singlets, 3H, CH_3O. (h) Quartet (J = 14.5, 7.0 Hz), 4H, ethoxy-CH_2. (i) Triplet (J = 7.0 Hz), 6H, ethoxy-CH_3. (j) Singlet, 2H, quinone-H. (k) Multiplet, 4H, aromatic. (l) Singlet, 1H, H-3. (m) Multiplet, 10H, aromatic. (n) Singlet, 2H, quinone-H. (o) Multiplet, each 2H, aromatic-H on the naphthoquinone.

Table II

^{13}C-Nmr Data of 5,6,7,8-Tetrahydroindolizines (a)

Compound	CH_3 (q)	C-7 (t)	C-6 (t)	C-8 (t)	C-5 (t)	C-1,2 (s)	C-3,8a (s)	*C*=O (s)		R		
6	10.55	19.24	22.89	23.54	41.18	119.47 121.26	133.27 135.62	192.60 193.33	127.59	128.24 128.40	130.91 131.16	140.74 140.98 (b)
8	10.31	19.24	22.90	23.39	43.21	109.81 112.57	132.38 135.31	165.44 166.41	51.00 51.33 (c)			
9	10.31	19.90	22.90	23.39	43.21	110.05 112.81	132.06 135.06	165.03 166.09	14.29 (d)	59.69 60.01 (e)		
10	10.51	19.19	22.56	23.62	42.85	115.29 116.30	134.97 136.68	182.21 182.86	139.93 (f)			
11	10.71	19.24	22.48	23.86	42.94	116.23 117.20	135.22 135.95	180.10 180.83	126.21 126.45	132.37 136.92 (g)	136.92	
13	--	20.05	22.97	22.97	46.02	119.71 124.99	125.39 (h) 136.43 (i)	190.65 192.68	127.83 128.48	127.83 128.48	128.64 131.32	139.60 140.49 (b)
15	--	19.56	22.73	23.62	46.34	117.28 122.07	122.56 (h) 135.46 (i)	180.26 180.42	126.53	132.46 132.86	136.11 137.57 (g)	

(a) In parts per million, from internal tetramethylsilane in deuteriochloroform. Parentheses indicate splitting patterns in the partial proton decoupling measurements. (b) Benzene-ring carbons of the benzoyl groups. (c) Methoxy carbons. (d) Methyl carbons of the ethoxy groups. (e) Methylene carbons of the ethoxy groups. (f) Ethylenic carbons of the *p*-quinone ring. (g) Benzene-ring carbons of the 1,4-naphthoquinone ring. (h) Doublet, C-3. (i) Singlet, C-8a.

as dimethyl and diethyl acetylenedicarboxylate, *p*-benzoquinone and 1,4-naphthoquinone afforded the corresponding tetrahydroindolizines **8**, **9**, **10** and **11**, in which no 1:1 adduct has been isolated (Table I and II). In the reaction of **2** with *p*-benzoquinone was obtained a 7.3% yield of the dihydroindolizine **12** in addition to **10**. This is probably due to dehydrogenation by *p*-benzoquinone employed in excess; **10** underwent dehydrogenation on treatment with *p*-benzoquinone or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone to form **12** exclusively.

8

9

10

11

12

For comparison and spectral assignment, the similar compounds of **13-16** were prepared from the reactions of 1-formylpiperidine-2-carboxylic acid (**17**) (8c).

13

14

15

16

17

Attempts to convert these tetrahydroindolizines to the corresponding aromatic indolizines under usual dehydrogenating conditions (Pd-C, DDQ and tetrachloro-*o*-benzoquinone) were so far unsuccessful.

EXPERIMENTAL

General.

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared spectra were obtained on a Jasco IR-G or a Hitachi EPI-G3 spectrophotometer. Visible and ultra-violet spectra were taken on a Hitachi 139 spectrophotometer. ^{1}H nmr spectra were measured on a JEOL 4H-100 instrument. ^{13}C nmr spectra were recorded on a JEOL FX-60 pulsed Fourier transformation nuclear magnetic resonance spectrometer operating at 15.040 MHz. Samples were observed in 10-mm.o.d. tubes, at 0.1-0.2 M solutions in deuteriochloroform at 30°. Chemical shifts are given in parts per million downfield from tetramethylsilane as zero. Partial proton decoupling was used to distinguish between individual carbon atoms. Mass spectra were obtained on a JEOL 01SG-2 mass spectrometer.

1,2-Dibenzoyl-3-methyl-5,6,7,8-tetrahydroindolizine (**6**) and 1,2-Dibenzoyl-3-methyl-5,6,7,8-tetrahydroindolizine-8a,3-carbolactone (**4**).

A solution of 1.0 g. (7.75 mmoles) of 2-piperidinecarboxylic acid (**2**) and 7.3 g. (31.0 mmoles) of dibenzoylacetylene was heated at 70° in 120 ml. of acetic anhydride for 72 hours. After evaporation of acetic anhydride *in vacuo*, the products were isolated by column chromatography on silica-gel with benzene-chloroform as eluent, and successively purified by silica-gel preparative thin layer chromatography (*n*-hexane-ether). From the first fraction, 300 mg. of a yellow amorphous product **4** (yield, 10%, m.p. 60-63°) was obtained; ir (potassium bromide disk): 1777, 1760, 1735, 1660 and 1630 cm^{-1} (carbonyl); pmr (deuteriochloroform): 1.7-2.2 (m, 4H, methylenes of the position 6 and 7), 2.13 (s, 3H, methyl), 2.76 (t, 2H, J = 6 Hz, methylene of the position 8), 4.34 (t, 2H, methylene of the position 5), 7.0-7.4 (m, 10H, aromatic); ^{13}C nmr (deuteriochloroform): 20.30 (q, methyl-carbon), 19.33, 20.95, 23.31 and 45.89 (each t, carbons of the position 7, 6, 8 and 5, respectively), 122.23 and 126.78 (each s, carbons of the position 3 and 8a) (10), 127.10-132.30 (complex peaks due to olefinic quaternary and aromatic carbons), 139.86 and 140.42 (s, aromatic carbons attached to carbonyl groups), 169.17 (s, carbon of the lactone ring) and 187.04 and 191.26 (each s, benzoyl-carbonyl carbons); ms: M^+ m/e 387, M^+-CO_2 m/e 343.

Anal. Calcd. for $C_{24}H_{21}O_4N$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.01; H, 5.58; N, 3.39.

From the second fraction, 1.16 g. of pale yellow crystals of **6** were obtained (Table I and II).

Dimethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (**8**).

A solution of 2.0 g. (15.5 mmoles) of **2** and 6.6 g. (46.5 mmoles) of dimethyl acetylenedicarboxylate was heated at 100° in 40 ml. of acetic anhydride for 4 hours. The product isolated in a similar workup as above was purified by a recrystallization from ethanol to give 1.09 g. of **8** (Table I and II).

Diethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylate (**9**).

In a similar manner as above for **8**, the treatment of 1.0 g. (7.75 mmoles) of **2** with 1.87 g. (11.6 mmoles) of diethyl acetylenedicarboxylate in 20 ml. of acetic anhydride at 100° for 6 hours gave 630 mg. of **9** (Table I and II).

5-Methyl-7,8,9,10-tetrahydrobenzo[*a*]indolizine-1,4-dione (**10**) and 5-Methyl-7,8-dihydrobenzo[*a*]indolizine-1,4-dione (**12**).

In a similar manner as above for **6**, the reaction of 1.0 g. (7.75 mmoles) of **2** with 1.2 g. (11.6 mmoles) of *p*-benzoquinone in 100 ml. of acetic anhydride at 80° for 6 hours gave, after successive isolations by silica-gel column chromatography with chloroform and silica-gel preparative thin layer chromatography with dichloromethane, and recrystallizations from ethanol, the following. From the upper fraction, 117 mg. (yield, 7.3%) of red crystals of **12**, m.p. 186-191°, was obtained; ir (potassium bromide disk): 1630 cm^{-1} (carbonyl); pmr (deuteriochloroform): 1.53-1.76 (m, 2H, methylene of the position 8), 2.59 (s, 3H, methyl), 3.94 (t, J = 7 Hz, 2H, methylene of the position 7), 6.62 (s, 2H, olefinic of the position 2 and 3), 6.15-6.33 (m, 1H, olefinic of the position 10), 7.03-7.21 (m, 1H, olefinic of the position 9); ms: M^+ m/e 213.

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.99; H, 5.38; N, 6.24.

From the lower fraction, 306 mg. of yellow crystals of **10** was obtained (Table I and II).

7-Methyl-9,10,11,12-tetrahydronaphtho[2,3-*a*]indolizine-1,6-dione (**11**).

A solution of 1.0 g. (7.75 mmoles) of **2** and 4.9 g. (31.0 mmoles) of 1,4-naphthoquinone was heated at 85° in 100 ml. of acetic anhydride for 23 hours. After evaporation of acetic anhydride *in vacuo*, the residue was chromatographed on silica-gel with benzene-chloroform as eluent affording 855 mg. of yellow crystals of **11** which was recrystallized from ethanol (Table I and II).

1,4-Diphenyl-5-methyl-7,8,9,10-tetrahydropyridazino[4,5-*a*]indolizine (**7**).

To a solution of 398 mg. (1.16 mmoles) of **6** in 30 ml. of ethanol was added dropwise 14.5 ml. of 100% hydrazine hydrate. After stirring and heating at 70° for 30 minutes the mixture was concentrated to *ca.* 10 ml. to give yellow crystals of **7** (68 mg., 17%), which was recrystallized from ethanol containing small portions of water, m.p. 235.0-241.5°; ir (potassium bromide disk): 1532 cm^{-1}; pmr (deuteriochloroform): 1.6-2.2 (m, 4H, methylenes of the position 8 and 9), 2.59 (t, J = 6 Hz, 2H, methylene of the position 10), 4.05 (t, 2H, methylene of the position 7), 7.3-7.8 (m, 10H, aromatic); ms: M^+ m/e 339.

Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.21; H, 6.12; N, 12.11.

1,2-Dibenzoyl-5,6,7,8-tetrahydroindolizine (**13**).

A solution of 1.0 g. (6.4 mmoles) of 1-formylpiperidine-2-carboxylic acid (**17**) and 2.1 g. (9.0 mmoles) of dibenzoylacetylene was treated at room temperature in 30 ml. of acetic anhydride for 7 hours. After evaporation of acetic anhydride *in vacuo*, the residue was chromatographed on silica-gel with *n*-hexane-ether as eluent affording 1.47 g. (yield, 70%) of yellow crystals of **13** which was recrystallized from ethanol (Tables I and II).

7,8,9,10-Tetrahydrobenzo[*a*]indolizine-1,4-dione (**14**).

A solution of 1.0 g. (6.4 mmoles) of **17** and 2.1 g. (19.2 mmoles) of *p*-benzoquinone was heated at 100° in 10 ml. of acetic anhydride for an hour. The product isolated in a similar workup as above for **10** was recrystallized from ethanol to afford 64 mg. (yield, 5%) of **14** (Table I).

9,10,11,12-Tetrahydronaphtho[2,3-*a*]indolizine-1,6-dione (**15**).

A solution of 1 g. (6.4 mmoles) of **17** in 10 ml. of acetic anhydride was treated with 1.1 g. (7.0 mmoles) of 1,4-naphthoquinone at room temperature for 35 minutes. Precipitated crystals were washed with ethanol and recrystallized from benzene to give 540 mg. (yield, 34%) of yellow crystals of **15** (Tables I and II).

1,4-Diphenyl-7,8,9,10-tetrahydropyridazino[4,5-*a*]indolizine (**16**).

In a similar manner as above for **7**, the treatment of 200 mg. of **13** with excess hydrazine hydrate in 10 ml. of ethanol at 60° for 30 minutes gave 129 mg. (65%) of **16** which was recrystallized from ethanol containing small portions of water; m.p. 207-210°; ir (potassium bromide disk): 1537 cm^{-1}; pmr (deuteriochloroform): 1.6-2.2 (m, 4H, methylenes of the position 8 and 9), 2.62 (t, J = 6 Hz, 2H, methylene of the position 10), 4.30 (t, 2H, methylene of the position 7), 7.2-8.2 (m, 11H, aromatic-H of phenyl and the position 5); ms: M^+ m/e 325.

Anal. Calcd. for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.35; H, 5.84; N, 12.85.

Reaction of **2** with Chloro-*p*-benzoquinone.

In a similar manner as above for **6**, the treatment of 1.0 g. (7.75 mmoles) of **2** and 2.2 g. (15.5 mmoles) of chloro-*p*-benzoquinone in 10 ml. of acetic anhydride at 85° for 1.5 hours gave a mixture of the corresponding 5,6-dihydro- and 5,6,7,8-tetrahydroindolizines which were unable to separate by column or thin layer chromatography. Furthermore, since the orientation of this cycloaddition, *i.e.*, the position of chlorine in the products, could not be determined by the spectral methods, these products were not further examined.

The mixture had m.p. 175-185°; ir (potassium bromide): 1640, 1660 cm^{-1}; ms: m/e 249; pmr (deuteriochloroform): 1.67-2.20 (m, 4H), 3.10 (t, 2H), 3.83 (t, 2H), 2.51 (s, 3H), 6.82 (s, 1H).

Anal. Calcd. for $C_{13}H_{12}ClO_2N$: N, 5.61. Found: N, 5.51.

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