Diels-Alder Cycloadditions of Diene-Substituted *N*-Ethoxycarbonyl-2-methyl-1,2-dihydropyridines with *N*-Phenylmaleimide

Grant R. Krow*, Kevin C. Cannon, James T. Carey,
Yoon B. Lee, and Steven W. Szczepanski

Department of Chemistry, Temple University,
Philadelphia, PA 19122

Harri G. Ramjit

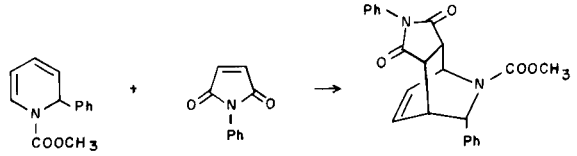
Merck Sharp and Dohme Research Laboratories,
West Point, PA 19486

Received May 3, 1984

The ten possible substitution patterns for *N*-ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5** in which one or two olefinic sites are alkyl substituted were synthesized and reacted with *N*-phenylmaleimide **2** to provide cycloadducts **6**. *N*-Ethoxycarbonyl-5,6-cyclohexyl-2-methyl-1,2-dihydropyridine **51** provided the novel spirocycle **61**.

J. Heterocyclic Chem., **22**, 131 (1985).

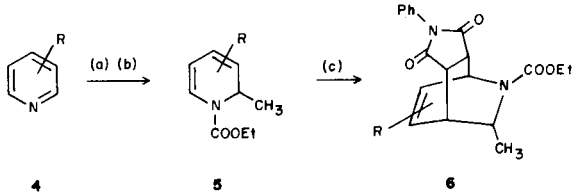
The structure of the Diels-Alder adduct of *N*-methoxycarbonyl-2-phenyl-1,2-dihydropyridine **1** and *N*-phenylmaleimide **2** has been shown to be the *N*-methoxycarbonyl-3-*endo*-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic acid *N*-phenylimide **3** [1]. To further explore the use of substituted *N*-acyl-1,2-dihydropyridines **5** as dienes for 4 + 2 cycloadditions [2,3] and to test the scope of methyl Grignard additions to substituted pyridines **4** as a source of *N*-alkoxycarbonyl-1,2-dihydropyridines **5** [4,5], we have prepared and characterized a number of *N*-phenylmaleimide cycloadducts **6**.



1 **2** **3**

To achieve the stated end shown in Scheme 1, the *N*-ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5** were prepared by reaction of methylmagnesium iodide with substituted pyridines **4** and the resultant addition products were trapped with ethyl chloroformate [4a]. The 1,2-dihydropyridines **5** thus prepared were reacted directly with *N*-phenylmaleimide **2** in refluxing methylene chloride or chloroform to provide the cycloadducts **6**.

Scheme I



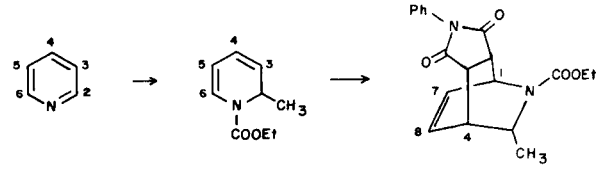
4 **5** **6**

(a) Methylmagnesium iodide (b) Ethyl chloroformate (c) *N*-phenylmaleimide

The 1,2-dihydropyridines **5a-d** (Table I) collectively have substituents at the four possible dienic positions of **5**, while the 1,2-dihydropyridines **5f-k** have representative examples of the six possible disubstitution patterns for the diene of **5**; *i.e.*, 3,4-, 3,5-, 3,6-, 4,5-, 4,6-, and 5,6-disubstitution. Additionally, 1,2-dihydropyridine **5e** was prepared from 2-benzylpyridine **4d**, which indicates that addition of methylmagnesium iodide to the pyridine ring can compete with abstraction of the doubly activated benzylic protons. The annelated 1,2-dihydropyridine **51** could be synthesized from 2,3-cyclohexanopyridine **4j**.

Table I

N-Phenylmaleimide Cycloadducts **6** from *N*-Ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5** Prepared from Substituted Pyridines **4**



4 **5** **6**

Pyridine **4**	Dihydropyridine **5**	Cycloadduct **6**
4a 2-Me	**5a** 6-Me	**6a** 1-Me
4b 3-Me	**5b** 3-Me	**6b** 4-Me [a]
	5c 5-Me	**6c** 7-Me [a]
4c 4-Me	**5d** 4-Me	**6d** 8-Me
4d 2-CH_2Ph	**5e** 6-CH_2Ph	**6e** 1-CH_2Ph
4e 2,3-di-Me	**5f** 5,6-di-Me	**6f** 1,7-di-Me
4f 2,4-di-Me	**5g** 4,6-di-Me	**6g** 1,8-di-Me
4g 5-Et, 2-Me	**5h** 3-Et, 5-Me	**6h** 4-Et, 1-Me
4h 3,4-di-Me	**5i** 3,4-di-Me	**6i** 4,8-di-Me [b]
	5j 4,5-di-Me	**6j** 7,8-di-Me [b]
4i 3,5-di-Me	**5k** 3,5-di-Me	**6k** 4,7-di-Me
4j 2,3-$(CH_2)_4$-	**5l** 5,6-$(CH_2)_4$-	**6l** 1,7-$(CH_2)_4$-

[a] Obtained as an 84:16 mixture of **6b** and **6c**. [b] Obtained as a 65:35 mixture of **6i** and **6j**.

Table II

Analytical and Physical Data for Compounds **6**

Compound	Substitution	Reaction Solvent	Conditions Time (hours)	Yield (%)	Mp °C	Molecular Formula	Analyses (%) Calcd./Found C	H	N
6a	1-Me	CH_2Cl_2	130	72	167-168 [a]	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90
							67.68	6.35	7.86
6b/6c	4-Me/7-Me	CH_2Cl_2	72	52	135-136 [b]	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90
							67.77	6.34	7.86
6d	8-Me	CCl_4	55	69	123-125 [c]	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90
							67.61	6.20	7.69
6e	1-CH_2Ph	CH_2Cl_2	300	89	155-156 [d]	$C_{26}H_{26}N_2O_4$	72.54	6.09	6.51
							72.27	6.18	6.42
6f	1,7-di-Me	CCl_4	208	25	149-150 [a]	$C_{21}H_{24}N_2O_4$	68.46	6.56	7.60
							68.13	6.62	7.42
6g	1,8-di-Me	CCl_4	70	52	130-131 [e]	$C_{21}H_{24}N_2O_4$	68.46	6.56	7.60
							68.52	6.61	7.44
6h	4-Et, 1-Me	CCl_4	88	33	124-125 [e]	$C_{22}H_{26}N_2O_4$	69.09	6.85	7.32
							69.07	6.91	7.24
6i/6j	4,8-di-Me/-7,8-di-Me	CH_2Cl_2	168	60	136-137 [a]	$C_{21}H_{24}N_2O_4$	68.46	6.56	7.60
							68.28	6.77	7.45
6k	4,7-di-Me	CH_2Cl_2	210	94	100-101 [a]	$C_{21}H_{24}N_2O_4$	68.46	6.56	7.60
							68.45	6.63	7.48
6l	1,7-$(CH_2)_4$-	CH_2Cl_2	352	73	178-179 [b]	$C_{23}H_{26}N_2O_4$	70.03	6.64	7.10
							70.20	6.63	7.06

[a] From tetrahydrofuran/ether. [b] From tetrahydrofuran/petroleum ether. [c] From chloroform/hexane. [d] From tetrahydrofuran/pentane. [e] From ether/petroleum ether.

In two cases a single pyridine led to a pair of 1,2-dihydropyridines **5**. With 3-methylpyridine **4b** a mixture of 2,3- and 2,5-dimethyl-1,2-dihydropyridines **5b** and **5c** were formed, while the 3,4-dimethylpyridine **4h** the 2,3,4- and 2,4,5-trimethyl-1,2-dihydropyridines **5i** and **5j** resulted. Although we were unable to determine the ratios of these dihydropyridines, we did determine the ratios of the derived cycloadducts **6b/c** (86:14) and **6i/j** (65:35) by analysis of peak integrations of the relevant 360 MHz proton spectra (Table III). These ratios may not indicate the ratios of isomeric 1,2-dihydropyridines **5b/c** and **5i/j** afforded upon Grignard addition to the pyridines **4b** and **4h**, since the isolated yields of the cycloadducts **6** indicate some 1,2-dihydropyridine **5** was lost during the reaction with *N*-phenylmaleimide **2**.

The assigned structures **6a-l** were supported by microanalytical data shown in Table II and proton and ^{13}carbon nmr spectral data shown in Tables III and IV. A single stereoisomer of cycloadduct **6** was obtained in all cases, since only one set of ^{13}carbon nmr lines was observed for each cycloadduct. The stereochemistry of the cycloadducts **6** has been assigned on the basis of precedent with cycloadduct **3** [1a] as that having an *endo*-3-methyl group and an *endo*-5,6-dicarboxylic acid *N*-phenylimide; both are *syn* to the olefinic bridge of **6**. Mass spectra of the cycloadducts **6** showed an M^+-173 peak characteristic of cycloreversion and loss of *N*-phenylmaleimide **2**. A peak at m/e 116, which characterized an alternative cycloreversion with loss of a $CH_3CH{=}NHCOOEt^+$ fragment, was significant only when C-1 of adducts **6** was alkyl substituted as in **6a**, **6e**, **6h**, and **6l**; nevertheless, the m/e 116 peak was insignificant in the mass spectra of **6f** and **6g**.

Although cycloadducts **6** were formed in all cases, of special interest are adducts **6e**, **6h**, and **6l**, which show that 1-benzyl, 1-ethyl, and 1,7-tetramethylene groups do not inhibit cycloaddition. Adduct **6l** is also novel in having a spiro carbon at the bridgehead adjacent to nitrogen [6]. The ease of preparation of *N*-ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5** by reaction of methylmagnesium iodide with substituted pyridines **4**, and the ability to form cycloadducts **6** with 1,2-dihydropyridines **5** having mono- or dialkylation on the diene moiety, combine to broaden the scope of known 1,2-dihydropyridine cycloadditions. Further studies are underway to test the reactivity and stereochemical outcome of substituted 1,2-dihydropyridines **5** reacting with other dienophiles [3].

EXPERIMENTAL

Infrared spectra were measured with a Perkin-Elmer 137 sodium chloride spectrophotometer. Elemental analyses were performed by Micro Analysis, Inc., Wilmington, Delaware and Micro-Tech Laboratories, Inc., Skokie, Illinois. Proton nmr spectra were obtained in deuteriochloroform solutions with tetramethylsilane as an internal standard by using a Perkin-Elmer R-32 90 MHz spectrometer and a Varian XL-100-15 spec-

Table III

^{1}H-NMR Spectral Data of Compounds **6**

Compound	H-1	H-3x	H-4	H-5	H-6	H-7	H-8	Other [a]
6a		3.83 (dq) J = 6 Hz, 2 Hz	3.10 (m)	3.05 (m)	3.37 (d) J = 8 Hz	6.05 (d) J = 8 Hz	6.30 (dd) J = 8 Hz, 7 Hz	2.09 (Me)
6b	5.20 (m)	3.42 (m)		2.65 (d) J = 8 Hz	3.33 (dd) J = 7 Hz, 4 Hz	6.40 (dd) J = 7 Hz, 6 Hz	6.05 (d) J = 7 Hz	1.50 (Me)
6c	5.04 (m)	3.72 (m)	3.16 (m)	3.04 (dd) J = 8 Hz, 3 Hz	3.40 (m)		5.95 (d) J = 6 Hz	1.89 (Me)
6d	5.17 (m)	3.75 (m)	3.05 (m)	3.05-3.35 (m)	3.05-3.35 (m)	6.05 (d) J = 8 Hz		1.85 (Me)
6e		3.87 (m)	3.00 (m)	3.18 (m)	3.61 (d) J = 7 Hz	6.28 (m)	6.28 (m)	4.60 (d)/3.66 (d) J = 17 Hz (CH_2Ph)
6f		3.82 (dq) J = 7 Hz, 2 Hz	3.10 (m)	3.10 (m)	3.40 (d) J = 8 Hz		6.01 (d) J = 7 Hz	1.81 (Me) 2.15 (Me)
6g		3.85 (dq) J = 7 Hz, 3 Hz	3.20-2.95 (br)	3.20-2.95 (br)		5.69 (br)		2.07 (Me), 1.85 (d) (Me) J = 2 Hz
6h		3.78 (q) J = 8 Hz		2.98 (d) J = 7 Hz	3.45 (d) J = 7 Hz	5.93 (d) J = 8 Hz	5.85 (d) J = 8 Hz	2.09 (Me), 1.38-0.85 (5H)
6i	5.16 (m)	3.51 (m)		2.76 (d) J = 8 Hz	3.36 (m)	6.11 (d) J = 7 Hz	6.40 (dd) J = 7 Hz, 6 Hz	1.81 (Me) 1.59 (Me)
6j	4.98 (m)	3.76 (m)	3.01 (m)	3.09 (dd) J = 8 Hz, 4 Hz	3.36 (m)			1.83 (Me) 1.81 (Me)
6k	5.02 (m)	3.40 (m)		2.68 (d) J = 8 Hz	3.40 (m)		5.63 (s)	1.87 (Me) 1.48 (Me)
6l		3.85 (dq) J = 6 Hz, 2 Hz	3.10 (m)	2.65 (m)	3.46 (d) J = 8 Hz		5.95 (d) J = 6 Hz	2.65 (m, 1H), 2.20 (m, 2H) 1.60 (m, 5H)

[a] Ph, δ 7.5-7.1 (m); CH_3CH_2O-, δ 4.18-4.10 (q, J = 7 Hz) and 1.20-1.15 (t, J = 7 Hz); C-3-Me, δ 1.14-1.09 (d, J = 6 Hz)

trometer fitted with a Nicolet FT computer. High-resolution (360 MHz) nmr spectra were recorded at the University of Pennsylvania Middle Atlantic nmr facility, G. McDonald, director. The ^{13}C-nmr spectra were recorded on a Varian XL-100 instrument operating at 25.2 MHz using a Nicolet NTCFT 1180 pulse system. Samples were measured in 5 mm tubes in deuteriochloroform solution with a deuterium pulse lock; deuteriochloroform was assigned as 76.9 ppm as the standard; chemical shifts were computer generated. Carbon peak multiplicities were determined by performing off-resonance experiments; peak assignments were made using chemical shift and peak multiplicity information combined with expected substituent effects upon alkyl substitution [7]. Exact mass measurements were taken on an RMH-2 Hitachi Perkin-Elmer or a VG Micromass 7035 mass spectrometer at an ionization energy of 70 eV at the University of Pennsylvania Mass Spectrometry Center, D. T. Terwilliger, director, or by Harri Ramjit, Merck, Sharp and Dohme Research Laboratories, West Point, PA. Routine mass spectra were obtained by R. Dumphy on a Perkin-Elmer RMU-6H mass spectrometer. Dry-column chromatography was performed by using Woelm dry column silica gel (activity III) with a fluorescent indicator. Thin-layer chromatography was conducted by using Analtech silica gel GF plates containing a fluorescent indicator.

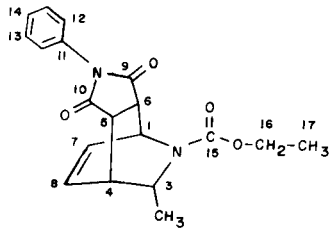
The substituted pyridines, 2,4-lutidine, 3,4-lutidine, 3,5-lutidine, 2-picoline, 3-picoline, 4-picoline, 2-benzylpyridine, 5-ethyl-2-methylpyridine, and 2,3-cyclohexenopyridine were purchased from Aldrich Chemical Company; 2,3-lutidine was purchased from Fairfield Chemical Company.

N-Ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5**. General Procedure.

To a stirred suspension of 0.483 g (20 mmoles) of dried magnesium turnings in 20 ml of ether in a 50 ml flask maintained under a nitrogen atmosphere, 2.84 g (20 mmoles) of methyl iodide was added dropwise at such a rate that a gentle reflux was maintained. After addition was complete and the exothermic reaction had ceased, the reaction mixture was cooled to 0° and the appropriate alkyl substituted pyridine (20 mmoles) in 15 ml of ether was added dropwise. After completion of addition, 2.16 g (20 mmoles) of ethyl chloroformate was added dropwise. Following stirring for 30 minutes, the reaction mixture was transferred to a separatory funnel to which 30 ml of water and 30 ml of ether were added. The organic layer was separated and the aqueous layer was washed twice with ether. After drying over magnesium sulfate, the solvent was removed from the combined organic layers *in vacuo*. The residue was chromatographed on a silica gel column with 1:1 cyclohexane-ether as eluent to afford the *N*-ethoxycarbonyl-2-methyl-1,2-dihydropyridines **5** as oils; isolated yields were: **5a** (56%), ms: m/e 181 (M^+); **5b/5c** (94%), ms: m/e 181 (M^+); **5d** (41%), ms: m/e 181 (M^+); **5e** (30%), ms: m/e 257 (M^+); **5f** (73%), ms: m/e 195 (M^+); **5g** (98%), ms: m/e 195 (M^+); **5h** (79%), ms: m/e 209 (M^+); **5i/5j** (83%), ms: m/e 195 (M^+); **5k** (78%), ms: m/e 195 (M^+); **5l** (65%), ms: m/e 221 (M^+). Efforts to detect *N*-ethoxycarbonyl-4-methyl-1,4-dihydropyridines by looking for the characteristic peak of the doubly allylic H-4 proton between δ 2.80-3.00 [3b] generally indicated no more than traces of 1,4-addition product. The dihydropyridines from 2-methylpyridine **4a** and the annelated pyridine **4j** provided nmr spectra with absorption between δ 2.8-3.00. However, no attempt was made to isolate or identify a 1,4-dihydropyridine since the 1,4-dihydropyridines do not interfere with the subsequent isolation of cycloadducts **6**. The 1,2-dihydropyridines **5**

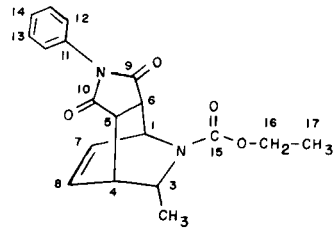
Table IV

^{13}C-NMR Spectral Data of Compounds **6**



Carbon	Compound **6a**	**6b**	**6c**	**6d**
C-1	55.81 (s)	46.43 (d)	51.53 (d) [a]	47.69 (d)
C-3	56.29 (d)	57.71 (d)	52.81 (d) [a]	52.13 (d)
C-4	39.10 (d)	42.12 (s)	39.63 (d)	41.12 (d)
C-5	42.99 (d)	45.35 (d) [a]	42.00 (d)	44.44 (d) [a]
C-6	48.46 (d)	46.17 (d) [a]	44.21 (d)	45.08 (d) [a]
C-7	136.89 (d)	136.73 (d)	140.56 (s)	122.31 (d)
C-8	130.95 (d)	129.42 (d)	123.12 (d)	141.60 (s)
C-9/10	175.82 (s)	174.99 (s)	176.21 (s)	175.97 (s)
	173.95 (s)	173.83 (s)	131.73 (s)	131.79 (s)
C-11	131.76 (s)	131.68 (s)	131.73 (s)	131.79 (s)
C-12/13	128.41 (d)	128.46 (d)	128.61 (d)	128.69 (d)
	125.95 (d)	125.96 (d)	125.96 (d)	126.02 (d)
C-14	128.13 (d)	128.00 (d)	128.13 (d)	128.21 (d)
C-15	156.01 (s)	154.23 (s)	154.71 (s)	154.59 (s)
C-16	60.91 (t)	60.94 (t)	61.00 (t)	60.99 (t)
C-17	14.56 (q)	14.25 (q)	14.30 (q)	14.36 (q)
C-1-Me	23.90 (q) [a]			
C-3-Me	20.51 (q) [a]	15.58 (q) [b]	19.02 (q) [b]	18.84 (q) [b]
C-4-Me		17.98 (q) [b]		
C-7-Me			19.52 (q) [b]	
C-8-Me				21.83 (q) [b]

Table IV (Continued)



Carbon	Compound **6i**	**6j**	**6k**	**6l**
C-1	47.14 (d)	45.52 (d)	51.47 (d)	59.84 (s)
C-3	57.64 (d)	52.63 (d)	58.38 (d)	56.23 (d)
C-4	44.60 (s)	41.85 (d)	42.78 (s)	42.63 (d)
C-5	45.61 (d) [a]	44.89 (d) [a]	46.57 (d) [a]	47.04 (d)
C-6	46.23 (d) [a]	45.52 (d) [a]	46.23 (d) [a]	47.04 (d)
C-7	122.29 (d)	131.18 (s)	139.45 (s)	145.24 (s)
C-8	143.52 (s)	130.18 (s)	128.62 (d)	122.10 (d)
C-9/10	175.20 (s)	176.17 (s)	175.24 (s)	176.32 (s)
	173.99 (s)	174.15 (s)	173.78 (s)	131.97 (s)
C-11	131.76 (s)	131.81 (s)	132.03 (s)	174.12 (s)
C-12/13	128.58 (d)	128.66 (d)	128.62 (d)	128.66 (d)
	126.02 (d)	126.04 (d)	126.14 (d)	126.18 (d)
C-14	128.08 (d)	128.12 (d)	128.13 (d)	128.15 (d)
C-15	154.25 (s)	154.66 (s)	154.63 (s)	146.26 (s)
C-16	60.91 (t)	60.92 (t)	61.08 (t)	60.65 (t)
C-17	14.32 (q)	14.33 (q)	14.38 (q)	14.31 (q)
C-1-Me				[e]
C-3-Me	16.01 (q) [b]	15.79 (q) [b]	18.18 (q) [b]	16.81 (q)
C-4-Me	15.50 (q) [b]		15.77 (q) [b]	
C-7-Me		17.83 (q) [b]	19.51 (q) [b]	[e]
C-8-Me	18.77 (q) [b]	18.81 (q) [b]		

[a], [b] The indicated chemical shift assignments can be interchanged. [c] C-1-CH_2Ph 38.47 (t), 131.54 (s), 128.63 (d), 128.98 (d), 125.59 (d). [d] C-4-CH_2CH_3 23.60 (t), 7.14 (q). [e] C-1,7-$(CH_2)_4$- 24.88 (t), 26.88 (t), 20.27 (t), 19.26 (t).

Table IV (Continued)

Carbon	Compound **6e**	**6f**	**6g**	**6h**
C-1	59.08 (s)	59.10 (s)	56.93 (s)	55.91 (s)
C-3	56.57 (d)	56.04 (d)	55.67 (d)	57.81 (d)
C-4	39.01 (d)	38.97 (d)	42.67 (d)	44.86 (s)
C-5	42.66 (d)	42.81 (d)	44.05 (d)	42.75 (d)
C-6	47.75 (d)	49.32 (d)	48.76 (d)	50.18 (d)
C-7	134.85 (d)	142.97 (s)	128.71 (d)	136.23 (d) [a]
C-8	131.04 (d)	124.90 (d)	140.77 (s)	136.70 (d) [a]
C-9/10	175.83 (s)	176.38 (s)	176.02 (s)	174.81 (s)
	174.24 (s)	174.22 (s)	174.22 (s)	132.00 (s)
C-11	131.71 (s)	131.97 (s)	131.93 (s)	132.00 (s)
C-12/13	128.59 (d)	128.77 (d)	128.71 (d)	128.73 (d)
	126.07 (d)	126.20 (d)	126.15 (d)	126.32 (d)
C-14	128.14 (d)	128.27 (d)	128.18 (d)	128.26 (d)
C-15	156.54 (s)	156.24 (s)	156.26 (s)	156.52 (s)
C-16	60.83 (t)	60.70 (t)	60.63 (t)	60.94 (t)
C-17	14.13 (q)	14.35 (q)	14.29 (q)	14.45 (q)
C-1-Me	[c]	20.39 (q) [a]	23.56 (q) [a]	23.93 (q)
C-3-Me	19.70 (q)	18.23 (q)	19.83 (q)	16.60 (q)
C-4-Me				[d]
C-7-Me		20.15 (q) [a]		
C-8-Me			21.46 (q) [a]	

were further characterized as the corresponding *N*-phenylmaleimide cycloadducts **6**.

2-(Ethoxycarbonyl)-3-*endo*-methyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimides **6**. General Procedure.

A stirred solution of 2.7-17 mmoles of the crude *N*-ethoxycarbonyl-2-methyl-1,2-dihydropyridine **5** and one equivalent of *N*-phenylmaleimide in 5-80 ml of dry dichloromethane or carbon tetrachloride was refluxed for the indicated time in Table II under an inert argon atmosphere. After cooling, solvent was removed *in vacuo* and the residue was chromatographed on Analtech silica gel GF thin-layer plates, Woelm dry column silic gel, or Silica Gel 60 (Merck) to provide **6**.

2-(Ethoxycarbonyl)-1,3-*endo*-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic Acid *N*-phenylimide (**6a**).

From 549 mg (3.03 mmoles) of a dihydropyridine mixture containing *N*-ethoxycarbonyl-2,6-dimethyl-1,2-dihydropyridine **5a** and 525 mg (3.03 mmoles) of *N*-phenylmaleimide **2** there was obtained 775 mg (72%) of a white solid **6a** (Table II); ir (chloroform): 1710 cm^{-1}; chemical ionization ms: m/e 335.1661 (M^+ + 1, 61), 181 (72), 166 (100), 116 (35), 94 (42).

2-(Ethoxycarbonyl)-3-*endo*-4-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarbocyclic Acid *N*-Phenylimide (**6b**) and 2-(Ethoxycarbonyl)-3-*endo*-7-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6c**).

From 2.92 g (17.1 mmoles) of a dihydropyridine mixture containing *N*-ethoxycarbonyl-2,3-dimethyl-1,2-dihydropyridine **5b** and *N*-ethoxycarbonyl-2,5-dimethyl-1,2-dihydropyridine **5c** with 1.84 g (17.1 mmoles) of **2** there was obtained 3.02 g (52%) of a white solid consisting of cycloadducts **6b** and **6c** in a ratio of 86:14 by nmr analysis (Table II); ir (chloroform): 1710 cm^{-1}; chemical ionization ms: m/e 335.1658 (M^+ + 1, 59), 181 (74), 166 (100), 94 (36).

2-(Ethoxycarbonyl)-3-*endo*-8-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6d**).

From 1.48 g (8.2 mmoles) of *N*-ethoxycarbonyl-2,4-dimethyl-1,2-dihydropyridine (**5d**) and 1.42 g (8.2 mmoles) of **2** there was obtained 1.99 g (69%) of **6d** as a pale yellow solid (Table II); ir (chloroform): 1710 cm^{-1}; ms: m/e 354.1581 (M^+), 181 (32), 166 (100), 94 (26).

2-(Ethoxycarbonyl)-1-benzyl-3-*endo*-methyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6e**).

From 478 mg (1.86 mmoles) of *N*-ethoxycarbonyl-6-benzyl-2-methyl-1,2-dihydropyridine (**5e**) and 321 mg (1.86 mmoles) of **2** there was obtained 123 mg of **5e** and 489 mg (61%) of **6e** as a white solid (Table II); ir (chloroform): 1710 cm^{-1}; chemical ionization ms: m/e 431.1975 (M^+ + 1, 60), 257 (56), 242 (59), 116 (100), 91 (25).

2-(Ethoxycarbonyl)-1,3-*endo*-7-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic Acid *N*-Phenylimide (**6f**).

From 1.027 g (5.26 mmoles) of *N*-ethoxycarbonyl-2,5,6-trimethyl-1,2-dihydropyridine (**5f**) and 911 mg (5.26 mmoles) of **2** there was obtained 86 mg (8%) of **5f** and 451 mg (23%) of crystalline white solid **6f** (Table II); ir (chloroform): 1706 cm^{-1}; ms: m/e 368 (M^+), 195 (50), 180 (100), 108 (26).

2-(Ethoxycarbonyl)-1,3-*endo*-8-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6g**).

From 1.0 g (5.13 mmoles) of *N*-ethoxycarbonyl-2,4,6-trimethyl-1,2-dihydropyridine (**5g**) and 0.89 g (5.13 mmoles) of **2** there was obtained 974 mg (52%) of **6g** as a white crystalline solid (Table II); ir (chloroform): 1690 cm^{-1}; ms: m/e 368 (M^+), 195 (37), 180 (100), 108 (30).

2-(Ethoxycarbonyl)-4-ethyl-1,3-*endo*-dimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6h**).

From 1.50 g (7.17 mmoles) of *N*-ethoxycarbonyl-3-ethyl-2,6-dimethyl-1,2-dihydropyridine (**5h**) and 1.24 g (7.17 mmoles) of **2** there was obtained 393 mg of **5h** and 669 mg (24%) of **6h** as a white solid (Table II); ir (chloroform): 1700 cm^{-1}; ms: m/e 328 (M^+, 35), 209 (35), 194 (100), 166 (52), 116 (40).

2-(Ethoxycarbonyl)-3-*endo*-4,8-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6i**) and 2-(Ethoxcyarbonyl)-3-*endo*-7,8-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6j**).

From 1.046 g (5.36 mmoles) of a dihydropyridine mixture containing *N*-ethoxycarbonyl-2,3,4-trimethyl-1,2-dihydropyridine (**5i**) and *N*-ethoxycarbonyl-2,4,5-trimethyl-1,2-dihydropyridine (**5j**) with 928 mg (5.36 mmoles) of **2** there was obtained 1.209 g (60%) of a pale yellow solid consisting of **6i** and **6j** in a ratio of 65:35 by nmr analysis (Table II); ir (chloroform): 1685 cm^{-1}; chemical ionization ms: m/e 369.1805 (M^+ + 1, 63), 195 (60), 180 (100), 116 (5), 108 (70).

2-(Ethoxycarbonyl)-3-*endo*-4,7-trimethyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboxylic Acid *N*-Phenylimide (**6k**).

From 377 mg (1.93 mmoles) of *N*-ethoxycarbonyl-2,3,5-trimethyl-1,2-dihydropyridine (**5k**) and 334 mg (1.93 mmoles) of **2** there was obtained 668 mg (94%) of **6k** as a white solid (Table II); ir (chloroform): 1690 cm^{-1}; chemical ionization ms: m/e 369.1825 (M^+ + 1, 75), 195 (77), 180 (100), 116 (8), 108 (90).

9-(Ethoxycarbonyl)-10-*endo*-methyl-9-azatricyclo[6.2.2.$0^{3,8}$]dodec-2-ene-11,12-*endo*-dicarboxylic Acid *N*-Phenylimide (**6l**).

From 139 mg (0.80 mmoles) of **2** and 177 mg (0.80 mmoles) of *N*-ethoxycarrbonyl-2-methyl-5,6-tetramethylene-1,2-dihydropyridine (**5l**) there was obtained 45 mg of **5l** and 172 mg (55%) of **6l** as a white solid (Table II); ir (chloroform): 1685 cm^{-1}; chemical ionization ms: m/e 395.1978 (M^+ + 1, 59), 221 (74), 206 (100), 134 (34), 116 (25).

Acknowledgement.

This research was supported by Grant No. CA 24596, awarded by the National Cancer Institute, DHEW, and American Cancer Society Grant No. IN88J.

REFERENCES AND NOTES

[1a] G. R. Krow, J. T. Carey, D. E. Zacharias, and E. E. Knaus, *J. Org. Chem.*, **47**, 1989 (1982); [b] E. E. Knaus, F. M. Pasutto, C. S. Giam, and E. A. Swinyard, *J. Heterocyclic Chem.*, **13**, 481 (1976).

[2] For recent reviews: [a] U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972); [b] D. M. Stout and A. I. Meyers, *ibid.*, **82**, 223 (1982).

[3a] G. R. Krow, J. T. Carey, K. C. Cannon, and K. J. Henz, *Tetrahedron Letters*, 2577 (1982); [b] F. W. Fowler, *J. Org. Chem.*, **37**, 1321 (1977); [c] E. E. Knaus, K. Avasthi and C. S. Giam, *Can. J. Chem.*, **58**, 2447 (1980); [d] P. S. Mariano, M. E. Osborn, D. Dunaway-Mariano, B. C. Gunn and R. C. Pettersen, *J. Org. Chem.*, **42**, 2903 (1977); [e] T. Agawa and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 449 (1961); [f] P. A. Wender, J. M. Schaus and A. W. White, *ibid.*, **102**, 6157 (1980); [g] P. Mariano, G. Dunaway-Mariano and P. Huesmann, *J. Org. Chem.*, **44**, 124 (1979); [h] R. J. Sundberg and J. D. Bloom, *Tetrahedron Letters*, 5157 (1978); [i] C. Marazano, J.-L. Fourrey and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 37 (1981); [j] M. Natsume and M. Ogawa, *Heterocycles*, **15**, 237 (1981), and prior references cited therein; [k] R. V. Stevens and J. R. Moran, ACS/CJS Chemical Congress, April 1-6, 1979; American Chemical Society; Washington, DC, 1979; ORGN 289; [l] P. S. Mariano, M. E. Osborn, D. Dunaway-Mariano, B. C. Gunn and R. C. Pettersen, *J. Org. Chem.*, **42**, 2903 (1977).

[4a] G. Frankel, J. W. Cooper and C. M. Fink, *Agnew. Chem. Int. Ed. Engl.*, **9**, 523 (1970); [b] R. E. Lyle and D. L. Comins, *J. Org. Chem.*, **41**, 3250 (1976); [c] R. E. Lyle, J. L. Marshall and D. L. Comins, *Tetrahedron Letters*, 1015 (1977); [d] M. G. El Din, E. E. Knaus and C. S. Giam, *Can. J. Chem.*, **60**, 1821 (1981).

[5] For *N*-acyl-1,4-dihydropyridines compare: [a] K. Akiba, Y. Iseki and M. Wada, *ibid.*, 429 and 3935 (1982); [b] K. Akiba, H. Matsuoka and M. Wada, *ibid.*, 4093 (1981); [c] E. Piers and M. Soucy, *Can. J. Chem.*, **52**, 2563 (1974); [d] D. L. Comins and A. H. Abdullah, *J. Org. Chem.*, **47**, 4315 (1982).

[6] Compare, W. Nagata, S. Hirai, K. Kawata and T. Okumura, *J. Am. Chem. Soc.*, **89**, 5046 (1967).

[7a] R. M. Silverstein, G. C. Bassler and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 4th Ed, John Wiley and Sons, New York, 1981, p 261; [b] I. Morishima and K. Yoshikawa, *J. Am. Chem. Soc.*, **97**, 2950 (1975).