2-AZABICYCLO[2.2.2]OCT-7-ENES. 1. SYNTHESIS FROM POLYSUBSTITUTED 1,2-DIHYDROPYRIDINES

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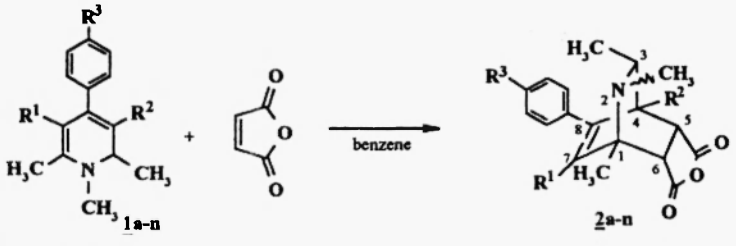
Abstract: Polysubstituted 1,2-dihydropyridines are found to undergo [4+2] cycloaddition as reactive dienes with maleic anhydride, dimethyl fumarate and methyl acrylate. Thermal reverse Diels-Alder reaction of azabicyclooctenes **2a** and **7** is demonstrated. Isomerization of 6-*exo*-methoxycarbonyl-2-azabicyclooctene **4** to 6-*endo*-diastereomer **5** upon treatment with *t*-BuOK is also shown.

Although 1,2-dihydropyridine (1,2-DHP) derivatives regarded as endocyclic 1-aminodienes undergo cycloaddition reactions offering a convenient access to functionalized 2-azabicyclo[2.2.2]oct-7-enes, the reactivity of 1,2-DHP containing electron-withdrawing groups (EWG) has been investigated only to a small extent. Herein we disclose our results of experiments intended to explore the utility of EWG substituted 1,2-DHP in Diels-Alder cycloaddition with some dienophiles.

Cycloaddition of 1,2-DHP **1** with maleic anhydride in benzene at 65 °C or under reflux afforded adducts **2**. Dihydropyridine **1a** and maleic anhydride gave azabicyclooctene **2a** in 39% yield under reflux, whereas the yield was 60% by performing the cycloaddition at 65 °C. A moderate yield of azabicyclooctenes is a consequence of the reverse [4+2] cycloaddition process. Facilitated by higher temperature (65–75 °C) decomposition of azabicyclooctene **2a** was also demonstrated (Fig.1).



The outcome of cycloadducts **2** depends upon the nature of 1,2-DHP substituents. The yields are decreased by EWG at 3-C of 1,2-DHP **1** (Table 1) whereas the formation of corresponding cycloadducts from 1,2-DHP **1b** and **1c** (R^1= R^2 = $COCH_3$, CN) did not proceed at all. The cycloaddition of 3-unsubstituted 1,2-DHP **1j-n** was not affected significantly by 4-aryl substituent (R^3= H, OCH_3, CH_3, Br, NO_2) whereas the reaction of dienes **1a,d-f, h**, containing EWG at 3-C was facilitated by electron-donating groups in the aryl moiety. This result is quite unexpected because the 4-aryl substituent and diene plane of 1,2-DHP molecule are almost perpendicular to one another [1], i.e. the 4-aryl substituent is out of conjugation.

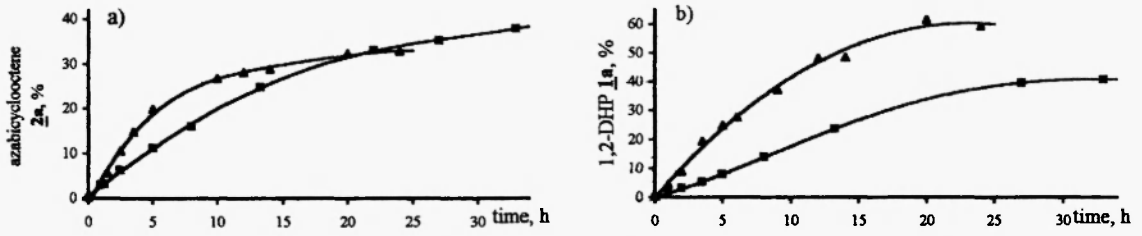


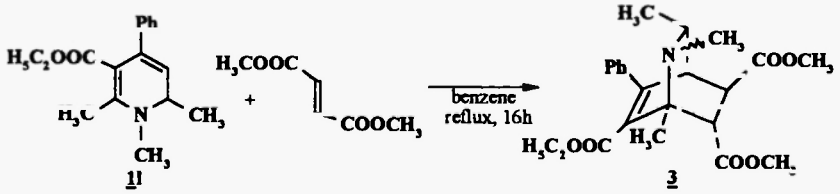
Figure 1. a) 2-azabicyclo[2.2.2]oct-7-ene **2a** formation from 1,2-DHP **1a** and maleic anhydride in benzene at 75 °C (▲) and 65 °C (■); b) 2-azabicyclo[2.2.2]oct-7-ene **2a** decomposition to 1,2-DHP **1a** in benzene at 75 °C (▲) and 65 °C (■).

Table 1. Formation of Diels-Alder cycloadducts **2** from 1,2-dihydropyridines **1**

	R^1	R^2	R^3	Yield, %	Reaction conditions
a	$COOC_2H_5$	$COOC_2H_5$	H	39	reflux, 16h
	$COOC_2H_5$	$COOC_2H_5$	H	60	65 °C, 16h
b	$COCH_3$	$COCH_3$	H	–	reflux, 16h; 65 °C, 16h
c	CN	CN	H	–	reflux, 16h; 65 °C, 16h
d	$COOC_2H_5$	$COOC_2H_5$	OCH_3	50	reflux, 8h
e	$COOC_2H_5$	$COOC_2H_5$	CH_3	41	reflux, 12h
f	$COOC_2H_5$	$COOC_2H_5$	Br	25	65 °C, 16h
g	$COOC_2H_5$	$COOC_2H_5$	NO_2	–	reflux, 16h; 65 °C, 16h
h	$COCH_3$	$COCH_3$	OCH_3	~2	65 °C, 16h
i	CN	CN	OCH_3	–	reflux, 20h; 65 °C, 25h
j	$COOC_2H_5$	H	OCH_3	57	reflux, 5h
k	$COOC_2H_5$	H	CH_3	65	reflux, 5h
l	$COOC_2H_5$	H	H	58	reflux, 5h
m	$COOC_2H_5$	H	Br	56	reflux, 5h
n	$COOC_2H_5$	H	NO_2	52	reflux, 5h

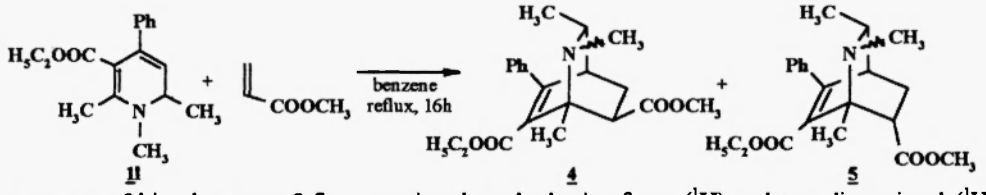
The assignment of 1,2-DHP and maleic anhydride cycloadducts **2** as 5,6-*endo*-isomers is in agreement with general principles of Diels-Alder reaction and is similar to the arrangement of substituents in 2-azabicyclooctene 5,6-*endo*-dicarboxylic acid imides [2].

Both 3,5-diethoxycarbonyl-1,2-DHP **1a** and 5-ethoxycarbonyl-1,2-DHP **1l** undergo cycloaddition with maleic anhydride. Less reactive dienophiles, i.e. dimethyl fumarate and methyl acrylate lead to cycloaddition product formation only with 1,2-dihydropyridine e.g. **1l** unsubstituted at 3-C atom.



The [4+2] cycloaddition proceeds stereospecifically as a *syn* process, and the formation of two diastereomers would be expected in the reaction of 1,2-DHP **1l** and dimethyl fumarate with respect to dienophile structure. Nevertheless, only one diastereomer **3** was isolated in a small yield (12%) besides unreacted 1,2-DHP.

The reaction of 1,2-DHP 1l with methyl acrylate afforded a mixture of cycloaddition products 4 and 5 in a low yield; ratio of isomers being 1 : 3.



The structure of bicyclooctenes 2-5 was assigned on the basis of one (^{1}H) and two dimensional (^{1}H,^{1}H)-COSY spectroscopy and confirmed by X-ray structure analysis of compound 3 [3].

Chemical shifts and coupling constants observed for compound 3 differ dramatically from these of unsubstituted 2-azabicyclooctene [4]. Consequently, the orientation of substituents could not be established in analogy with literature precedent. Protons 5-H and 6-H appear at 3.16 and 3.52 ppm respectively, the vicinal coupling constant is $^3J_{5,6}$= 6.0 Hz. The proton 5-H has an additional small constant $^3J_{4,5}$= 2.4 Hz caused by spin-spin interaction with *gauche*-positioned proton 4-H. Vicinal coupling constant $J_{5,6}$ smaller than this for *syn*-anhydride 2 indicates the *anticlinal* disposition of 5-H and 6-H protons of diester 3. The X-ray crystal structure (Fig.2) analysis of bicyclooctene 3 confirmed either the *anticlinal* arrangement of both COOMe groups or the *endo* location of the methyl group at 3-C as well as the *trans*-configuration of N-CH_3 and 3-CH_3 substituents. However, the disposition of N-substituent would be different in solution due to a possible nitrogen inversion.

Structure of stereoisomers 4 and 5 deserve the following comment. First, compared with the others, 3-H and 6-H protons are remarkably affected by different orientation of the COOMe group at 6-C. The signal of 3-H is downfield shifted (0.68 ppm) for 6-*endo*-ester 5. Second, the upfield shift (0.34 ppm) of 6-H_n compared with the corresponding 6-H_x of compound 5 is in analogy with the structure of 2-methyl-6-methoxycarbonyl-2-azabicyclooctenes [5].

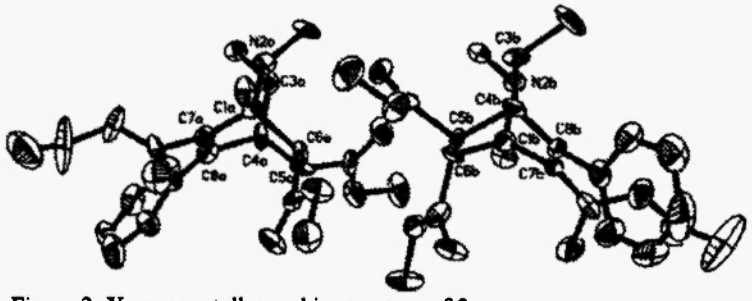
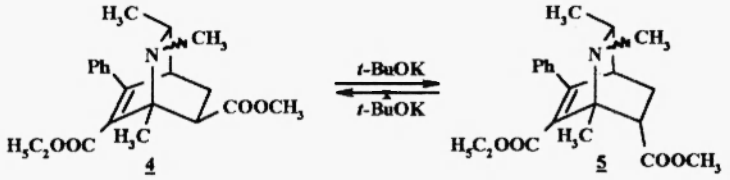


Figure 2. X-ray crystallographic structure of 3.

Rapid nitrogen inversion in N-methyl-2-azabicyclooctene (in NMR time-scale) was observed and the ratio of invertomers at ambient temperature is estimated by kinetic protonation [4]. Application of this method (addition of amine 5 to CF_3COOH solution in $CDCl_3$ followed by immediate recording of ^{1}H-NMR spectrum) to azabicyclooctene 5 revealed the presence of two protonated amine forms in solution. Consequently, the inversion of methyl group at nitrogen takes place. The methyl group at nitrogen of the quaternary amine salt appears as a doublet (3.04 ppm). According to the spectrum, the ratio of invertomers is 3 : 1. Probably, the 2-*exo*-methyl-2-azabicyclooctene (N-methyl and 3-methyl groups in *trans*-position) is predominant being thermodynamically more stable as compared with 2-*endo*-methyl invertomer (N-methyl and 3-methyl groups in *cis*-position).

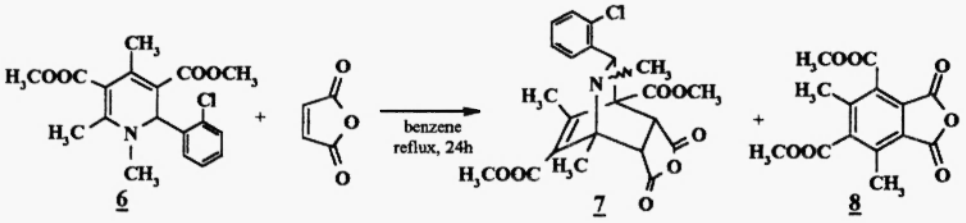
Treatment of 6-*exo*-methoxycarbonylazabicyclooctene **4** with *t*-BuOK in *t*-butanol led to 6-*endo*-diastereomer **5** formation through epimerization at the 6-C atom.



4 **5**

A complete isomerization with formation of epimer **5** in a quantitative yield was achieved by 2 eq of *t*-BuOK, whereas 1 eq of potassium butoxide caused isomerization only in 50% extent and 0.2 eq of the base did not initiate the isomerization process. Isomer **5** remained unchanged under these conditions. Predominant N-CH_3 group *syn* location to the ordinary $C_{(5)}$–$C_{(6)}$ bond induced the interaction between 2-CH_3 and 6-COOMe groups of compound **4**. Inversion at 6-C atom eliminates the steric hindrance responsible for ireversible epimerization of adduct **4** to isomer **5**.

Interaction of 2-(2'-chlorophenyl)-1,4,6-trimethyl-1,2-DHP **6** with maleic anhydride in benzene under reflux afforded Diels-Alder cycloadduct **7** in a low yield (11%). Besides the starting 1,2-DHP **6** an insignificant amount of phthalic anhydride derivative **8** was isolated from the reaction mixture.



6 **7** **8**

As it was showed above the reduced outcome of cycloadducts **2** was caused by reverse Diels-Alder reaction. The main destruction course of [4+2] cycloadducts is breakage of $C_{(1)}$–$C_{(6)}$ and $C_{(4)}$–$C_{(5)}$ bonds to produce the starting diene (dihydropyridine) and dienophile. Isolation of substituted phthalic anhydride **8** discloses an alternative path of reverse cycloaddition reaction including a breakage of $C_{(1)}$–N and $C_{(3)}$–$C_{(4)}$ bonds and leading to substituted 3a,7a-dihydroizobenzofuran-1,3-dione. The later is aromatized to phthalic anhydride **8** under reaction / isolation conditions.

Experimental

Melting points were determined on Boetius apparatus and are uncorrected. NMR spectra were recorded on a Brucker WH-90 or Varian Mercury 200 spectrometer, using deuterochloroform as a solvent, with tetramethylsilane as an internal standard. Column chromatography was performed on Across kiselgel 60 (0.063-0.200 mm). Elemental analysis data (C,H,N) of compounds prepared correspond to calculated values.

General procedure for the synthesis of 8-aryl-1,2,3-trimethyl-2-azabicyclo[2.2.2]oct-7-en-5,6-*endo*-dicarboxylic acid anhydrides 2. Maleic anhydride (0.15 g, 1.5 mmol) was added to a solution of 4-aryl-1,2,6-trimethyl-1,2-DHP **1** (1 mmol) in benzene (30 mL). The resulting solution was heated at 65 °C or refluxed. Reaction temperatures and times are indicated in Table 1. Then the solvent was removed *in vacuo* and the residue treated with diethyl ether afforded pure anhydrides **2**. Only compound **2h** was isolated by chromatography (ethyl acetate-hexane 1:2).

Dimethyl 7-ethoxycarbonyl-8-phenyl-1,2,3-trimethyl-2-azabicyclo[2.2.2]oct-7-en-5-*exo*-6-*endo*-5,6-dicarboxylate (3). Dimethyl fumarate (0.24 g, 1.7 mmol) was added to a solution of 1,2-DHP **1l** (0.30 g, 1.1 mmol) in benzene

Table 2. Spectroscopic and physical data of compounds **2a, d-f, h, j-n**

	M.p. (°C)	^{1}H-NMR data							
		1-CH_3, s, 3H	N-CH_3, s, 3H	3-CH_3, d, J=6.0Hz, 3H	3-H,[a] 1H	4-H, 1H	5-H, 1H	6-H, 1H	another groups signals[b]
2a	148-150	1.68	2.37	1.41	3.74	–	4.01, d, J = 10.2 Hz	3.18, d, J = 10.2 Hz	7.18, m, 2H and 7.28, m 3H (arom H)
2d	154-156	1.66	2.36	1.39	3.74	–	4.01, d, J = 10.2 Hz	3.15, d, J = 10.2 Hz	3.79 (s, 3H, OCH_3), 6.82 and 7.06 (d, J = 8.8 Hz, 2H, arom.H)
2e	155-156	1.66	2.37	1.41	3.76	–	4.02, d, J = 10.2 Hz	3.15, d, J = 10.2 Hz	2.31 (s, 3H, Ph-CH_3), 7.03 and 7.07 (d, J = 8.4 Hz, 2H, arom.H)
2f	148-150	1.66	2.37	1.38	3.74	–	4.01, d, J = 10.2 Hz	3.14, d, J = 10.2 Hz	6.99 and 7.43 (d, J = 8.4 Hz, 2H, arom H)
2h	146-148	1.83	2.39	1.40	3.63	–	3.79, d, J = 10.0 Hz	3.23, d, J = 10.0 Hz	1.54 (s, 6H, $COCH_3$), 3.82 (s, 3H, OCH_3), 6.87 and 7.00 (d, J=8.6 Hz, 2H, arom H)
2j		1.69	2.36	1.03	3.32-3.42, m, 2H		3.44, dd, J = 10.0, 3.6 Hz	3.05, d, J =10.0 Hz	3.82 (s, 3H, OCH_3), 6.88 and 7.25 (d, J = 8.8 Hz, 2H, arom H)
2k	146-148	1.67	2.36[c]	1.01	3.37, m, 2H		3.43, dd, J = 10.0, 3.6 Hz	3.06, d, J = 10.0 Hz	7.19 (m, 4H, arom.H)
2l	164-166	1.70	2.37	1.05	3.34-3.51, m, 2H		3.46, dd, J = 10.0, 3.8 Hz	3.07, d, J = 10.0 Hz	7.35 (m, 5H, arom H)
2m	149-150	1.67	2.37	1.01	3.32, m, 2H		3.47, dd, J = 10.0, 4.0 Hz	3.03, d, J = 10.0 Hz	7.18 and 7.51 (d, J = 8.4 Hz, 2H, arom.H)
2n	148-150	1.73	2.38	1.03	3.37, m, 2H		3.48, dd J = 10.0, 4.2 Hz	3.08, d, J = 10.0 Hz	7.48 and 8.25 (d, J = 8.6 Hz, 2H, arom H)

[a] **2a, d-f, h** – quadruplet, J = 6.0 Hz. [b] $COOC_2H_5$ for **2a, d-f, h** are at 0.85-0.99 ppm (t, J = 7.0 Hz, 3H) and 3.74-4.02 ppm (q, J = 7.0 Hz, 2H), for **2j-n** – 1.09-1.14 ppm (t, J = 7.0 Hz, 3H) and 4.12-4.15 ppm (q, J = 7.0 Hz, 2H). [c] Overlaps Ph-CH_3 signal.

(35 mL). The resulting mixture was refluxed for 16h, and then the solvent was removed *in vacuo*. The residue was treated with diethyl ether and the precipitate formed filtered off affording 0.27g of starting material 11. The other starting compound, i.e. dimethyl fumarate was precipitated by addition of hexane to filtrate. The remained filtrate evaporated and the oily residue obtained treated with hexane afforded 0.05 g (10%) of bicyclic compound 3, m.p. 122-123 °C (diethyl ether). ^{1}H-NMR: 0.91 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.12 (d, J = 6.4 Hz, 3H, $CHCH_3$), 1.44 (s, 3H, 1-CH_3), 2.37 (s, 3H, N-CH_3), 2.45 (dq, J = 6.0, 1.4 Hz, 1H, $CHCH_3$), 3.12 (m, 1H, 4-H), 3.16 (dd, J = 6.0, 2.4 Hz, 1H, 5-H), 3.52 (d, J = 6.0 Hz, 1H, 6-H), 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.96 (m, 2H, OCH_2CH_3), 7.26-7.37 ppm (m, 5H, arom.H).

7-Ethoxycarbonyl-6-methoxycarbonyl-8-phenyl-1,2,3-trimethyl-2-azabicyclo[2.2.2]oct-7-enes 4 and 5.

A solution of 1,2-DHP 11 (2.0 g, 7.4 mmol) and methyl acrylate (6.6 ml, 73.7 mmol) in benzene (50 mL) was refluxed for 16h. The reaction mixture evaporated and chromatographed (ethyl acetate-hexane 1:3) afforded the starting 1,2-DHP 11, *exo*-isomer 4 as a solid, m.p. 57-59 °C and *endo*-isomer 5 as a yellow thick oil. ^{1}H-NMR of *exo*-diastereoisomer 4: 1.02 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.07 (d, J = 6.0 Hz, 3H, 3-CH_3), 1.52 (s, 3H, 1-CH_3), 1.92 (ddd, J = 11.8, 11.0, 3.2 Hz, 1H, 5_n-H), 2.35 (ddd, J = 12.2, 5.0, 2.8 Hz, 1H, 5_x-H), 2.42 (s, 3H, N-CH_3), 2.67 (dd, J = 11.0, 5.0 Hz, 1H, 6-H), 2.80 (m, 1H, 4-H), 3.05 (dq, J = 6.2, 0.8 Hz, 1H, 3-H), 3.73 (s, 3H, OCH_3), 4.06 (m, 2H, OCH_2CH_3), 7.24-7.33 ppm (m, 5H, arom.H); ^{1}H-NMR of *endo*-diastereomer 5: 0.89 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.12 (d, J = 6.2 Hz, 3H, 3-CH_3), 1.44 (s, 3H, 1-CH_3), 1.94 (dd, J = 7.4, 3.0 Hz, 2H, 5-H), 2.35 (s, 3H, N-CH_3), 2.37 (m, 1H, 3-H), 2.69 (m, 1H, 4-H), 3.01 (t, J = 7.4 Hz, 1H, 6-H), 3.69 (s, 3H, OCH_3), 3.95 (m, 2H, OCH_2CH_3), 7.23-7.32 ppm (m, 5H, arom.H).

The isomerizaton of 6-*exo*-methoxycarbonyl-2-azabicyclo[2.2.2]oct-7-ene 4 with *t*-BuOK.

A solution of *t*-BuOK (1M, 1.6 mL) in tetrahydrofuran was added to a solution of 2-azabicyclooctene 4 (0.28 g, 0.8 mmol) in *t*-butanol (5 mL). The solution was stirred for 2.5 h at 50 °C, poured into ice water then extracted with chloroform. The chloroform solution was dried and evaporated to give 0.27 g (97%) of 6-*endo*-methoxycarbonyl-2-azabicyclooctene 5.

3-(2-Chlorophenyl)-4,7-dimethoxycarbonyl-1,2,8-trimethyl-2-azabicyclo[2.2.2]oct-7-en-5,6-*endo*-dicarboxylic acid anhydride (7). A solution of 1,2-DHP 6 (0.2 g, 0.53 mmol) and maleic anhydride (0.1 g, 1.02 mmol) in benzene (25 mL) was refluxed for 24h. The evaporated reaction mixture chromatographed (ethyl acetate-hexane 1:4) gave cycloadduct 7 (0.03 g, 11%), 5,7-dimethoxycarbonyl-4,6-dimethylisobenzofuran-1,3-dione (8) (0.005 g, 2%) and the starting 1,2-DHP 6 (0.18 g). ^{1}H-NMR of compound 7: 1.61 (s, 3H, 1-CH_3), 1.80 (s, 3H, 8-CH_3), 2.24 (s, 3H, N-CH_3), 3.46 (d, J = 9.0 Hz, 1H, 6-H), 3.63 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.12 (s, 1H, 3-H), 4.32 (d, J = 9.0 Hz, 1H, 5-H), 7.25 (m, 3H, arom.H), 7.41-7.57 ppm (m, 1H, arom.H); ^{1}H-NMR of compound 8: 2.51 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.88 ppm (s, 3H, OCH_3).

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