Tetrahedron Vol. 42, No. 11, pp. 2847 to 2853, 1986
Printed in Great Britain.

0040-4020/86 \$3.00+.00
Pergamon Journals Ltd.

AQUEOUS INTERMOLECULAR DIELS–ALDER CHEMISTRY

REACTION OF (*E*)-2,4-PENTADIENYL AMMONIUM CHLORIDE AND RELATED AMMONIUM SALTS WITH DIENOPHILES IN WATER

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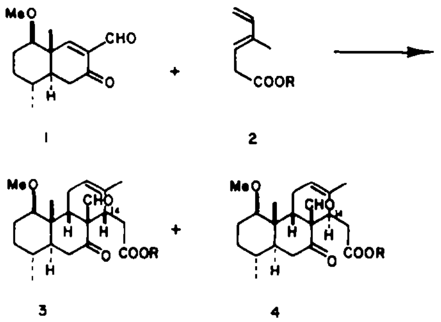
(*Received in U.S.A.* 2 *July* 1985)

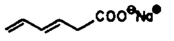
Abstract—The aqueous Diels–Alder reactions of a series of dienyl ammonium chlorides derived from (*E*)-2,4-pentadienyl amine, (*E*)-3,5-hexadienyl amine and (*E*)-4,6-heptadienyl amine with a variety of dienophiles have been examined. A similar Diels–Alder study employing the sodium salt of N-(*E*)-4,6-heptadienyl succinamic acid in water was also undertaken.

INTRODUCTION

Since the discovery that water can have a profound effect on both the rate and selectivity of the Diels–Alder reaction,[1] considerable efforts have been expended on probing the potential of aqueous Diels–Alder chemistry.[2] Notable among our early observations is the reaction of dienophile 1 with diene carboxylate 2 (R = Na^+).[1b] This reaction, which proceeds in water (4 h, 2.0 M in diene carboxylate, ambient temperature), gives rise to a 3 : 1 ratio of adducts 3 and 4 in near quantitative yield. In contrast, the reaction between dienophile 1 and diene 2 (R = Et) in benzene required 288 h in order to realize a 52% yield of 3 and 4 in a ratio of 1 : 1.2. It is of interest to note that there was a reversal in the selectivity in going from water to benzene.



As a direct consequence of these findings, we have investigated the reactions of sodium (*E*)-3,5-hexadienoate (**5**) and sodium (*E*)-4,6-heptadienoate (**6**) with a variety of dienophiles in water.[2a] Our findings revealed that, in general, Diels–Alder reactions proceeded rapidly in water at ambient temperature in good to excellent yield. Once again the data clearly demonstrated that the enhanced rates observed in aqueous medium stand in sharp contrast to the rates exhibited for the corresponding reaction in hydrocarbon solvents employing the corresponding methyl esters of **5** and **6**.



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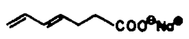

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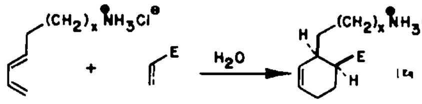
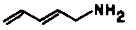
In order to appreciate fully the synthetic potential of aqueous Diels–Alder chemistry, we have examined the feasibility of incorporating cationic groups into the diene unit (cf. Eq. 1). Specifically we chose initially to investigate a series of dienyl ammonium chlorides derived from dienyl amines **7**–**9** in order to examine their reactivity with a variety of dienophiles. We were also curious to find what effect, if any, increasing the number of carbon atoms between the diene and ammonium group would have on reactivity.



(Eq. 1)



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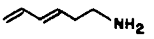

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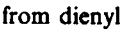
PREPARATION OF DIENYL AMINES

The synthesis of (*E*)-2,4-pentadienyl amine **7** commenced with the known (*E*)-2,4-pentadienyl bromide **10**[3], which was converted into **7** via a two-step sequence [(a) NaN_3, DMSO; (b) $LiAlH_4$, Et_2O, 0°] in 63% overall yield. (*E*)-3,5-Hexadienyl amine **8** and (*E*)-4,6-heptadienyl amine **9** were both synthesized from (*E*)-3,5-hexadienyl *p*-toluenesulfonate (**11**).[4] Displacement of tosylate **11** with sodium azide in dimethylsulfoxide gave rise to the corresponding azide, which upon reduction ($LiAlH_4$, Et_2O, 0°) provided dienyl amine **8** in 69% overall yield. Treatment of tosylate **11** with sodium cyanide in dimethylsulfoxide generated the corresponding nitrile, which upon reduction ($LiAlH_4$, Et_2O, 0°) afforded (*E*)-4,6-heptadienyl amine **9**.



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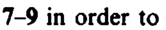

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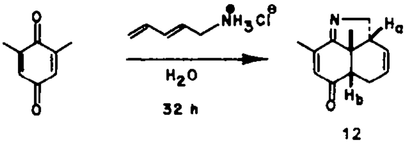
RESULTS AND DISCUSSION

With three representative dienyl amines in hand we turned our attention to aqueous Diels–Alder chemistry. Experimentally, the Diels–Alder reactions were conducted along the lines previously described by us.[2] Specifically, the diene was treated with an equivalent of a standardized solution of hydrochloric acid so as to give rise to a 2.0 M solution of amine hydrochloride in water. The reactions were generally conducted in the presence of a five-fold excess of dienyl amine hydrochloride.

Initial experiments concentrated on the reaction of (*E*)-2,4-pentadienyl ammonium chloride with substituted benzoquinones. Condensation of 2,6-dimethylbenzoquinone with 7·HCl in water at ambient temperature gave rise after 32 h to a 98% yield of the *cis* tricyclic imine **12**. The adduct obtained was that derived from an *endo* transition state with the anticipated *ortho* regiochemistry. None of the uncyclized free amino compound could be detected. The structure of the observed product follows from the IR and ^{1}H-NMR data. Additional proof of the structures was obtained from an NOE experiment. Irradiation of the angular methyl group gave rise to a 5% enhancement for each of the signals attributed to H_a and H_b. The reaction can be accelerated by warming the reaction mixture. For example, after 6.5 h at 50° a 61% yield of adduct **12** could be realized. Similar results were obtained with 2,5-dimethylbenzoquinone and 2-methyl-6-methoxybenzoquinone (Table 1). In the case of 2,5-dimethylbenzoquinone, where the reaction was sluggish at room temperature, requiring 120 h, heating at 50° resulted in a dramatic increase in reaction rate (11 h, 79% yield).



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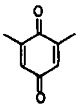
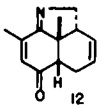
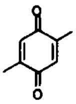
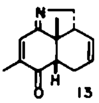
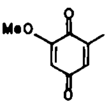
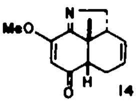
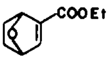
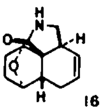
The absence of common dienophiles such as acrolein, methacrolein, methyl vinyl ketone and methyl acylate from Table 1 stems from the incompatability of the substrates with the acidic reaction medium. Only polymerization and 1,4-addition products were observed. In an attempt to overcome these difficulties, different counter-ions such as formate and borate were examined. However, again, no Diels–Alder adducts could be isolated. It is of interest to note that dienophile **15** (Table 1) reacts with 7·HCl in water giving rise to a 78% yield of crystalline lactam **16**, m.p. 201–202°. Attempts to react (*E*)-2,4-pentadienyl amine directly with dienophiles in either water or hydrocarbon solvents led to instantaneous polymer formation. This is not surprising in view of the tendency of amines to undergo facile 1,4-addition to Michael acceptors.

We next turned our attention to the reaction of (*E*)-3,5-hexadienyl ammonium chloride derived from **8** with our standard set of dienophiles. In the case of substituted benzoquinones, Table 2 reveals that the initially formed Diels-Alder adducts, as before, undergo facile, spontaneous transformation to cyclic imines. The most dramatic effect observed is the increase in reaction rate relative to the reaction rates obtained with (*E*)-2,4-pentadienyl ammonium chloride (Table 1). The enhanced rates seen with **8**·HCl may well be attributed to the fact that the ammonium residue is further removed from the diene unit, thus rendering it more reactive. Once again, use of dienophiles such as acrolein and methylvinyl ketone led to polymers.

The aqueous Diels–Alder adducts isolated after neutralization from the condensation of (*E*)-4,6-heptadienyl ammonium chloride with substituted benzoquinones (cf. **20** derived from **9**·HCl and 2,6-dimethylbenzoquinone) proved to be exceedingly sensitive and led to decomposition products.

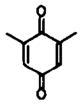
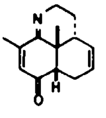
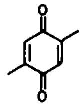
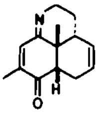
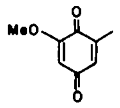
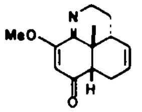
After the fact, this result is not surprising in view of

Table 1. Reaction of (*E*)-2,4-pentadienyl ammonium chloride with dienophiles[a]

Dienophile	Temp/°C	Time/h	Product	Yield %[b]
	25 50	32 6.5	 12	98 61
	25 50	120 11	 13	86 79
	25	20	 14	95
 15	25	23	 16	78

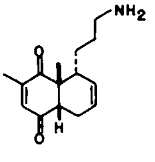
[a] All reactions were carried out 2.0 M in diene. A five-fold excess of diene was employed.
[b] Yields reported are for analytically pure materials.

Table 2. Reaction of (*E*)-3,5-hexadienyl ammonium chloride with substituted benzoquinones[a]

Dienophile	Time/h	Product	Yield % [b]
	2	 17	99
	21	 18	77
	1.75	 19	98

[a] All reactions were carried out 2.0 M in diene at 25°C. A five-fold excess of diene was employed.
[b] Yields reported are for analytically pure materials.

the many options which exist for the free amino group in adducts such as **20**. We could not detect any of the tricyclic imine adducts of type **21**. That Diels–Alder adducts were indeed formed in excellent yield was made obvious by trapping the free amine after neutralization with acetic anhydride. For example, the Diels–Alder adduct obtained from (*E*)-4,6-heptadienyl ammonium chloride and 2,5-dimethylbenzoquinone upon treatment with sodium carbonate and subsequent acetylation (Ac_2O, Et_3N) led to a 62% isolated yield of the *trans*-adduct **22**. As we have noted previously, the initially formed *cis*-adducts isomerize to the more stable *trans*-isomers.[2a]



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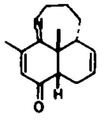

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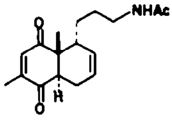

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In an effort to circumvent the problems created by the acidity of the aqueous medium containing the dienyl amine hydrochlorides, as well as the inherent instability of adducts such as **20**, we turned to the sodium salt of the N-dienyl succinamic acid **23**. Compound **23** was prepared in 75% yield by treatment of (*E*)-4,6-heptadienyl amine **9** with succinic anhydride in methylene chloride containing 4-dimethylaminopyridine.

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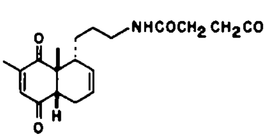
We examined the reaction of sodium N-(*E*)-4,6-heptadienyl succinamate in water with several dienophiles. As illustrated in Table 3, all reactions proceeded at ambient temperature in good to excellent yield. For comparison purposes, we condensed 2,6-dimethylbenzoquinone with methyl N-(*E*)-4,6-heptadienyl succinamate in toluene. At room temperature, 7 days were required to realize an 89% yield of Diels–Alder adduct **24**. Refluxing afforded after 8 h only a 44% yield of product.



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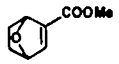
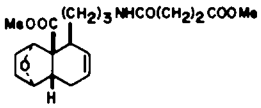
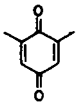
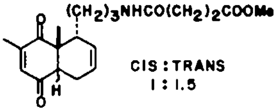
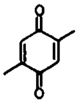
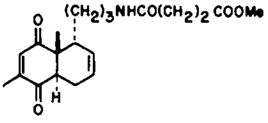
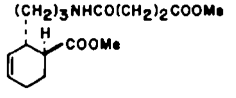
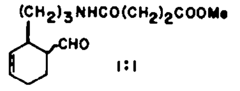
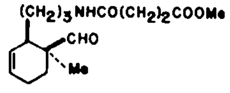
In summary, the aqueous Diels–Alder reaction employing (*E*)-2,4-pentadienyl ammonium chloride and related dienes gives rise to synthetically useful intermediates not hitherto available for use in organic synthesis. The acidic nature of the aqueous medium, however, is not compatible with sensitive dienophiles prone to polymerization. On the other hand, these problems can, in part, be eliminated by employing the corresponding N-dienyl succinamic acid sodium salt derivatives. One finds that dienophiles such as acrolein, methacrolein and methyl vinyl ketone are quite compatible with the essentially neutral conditions associated with using carboxylate salts.

EXPERIMENTAL

^1H-NMR spectra were taken at either 90 MHz (Varian EM-390), 220 MHz (Varian HR-200) or at 360 MHz (Nicolet NT-360) as indicated. Chemical shifts are reported in ppm (δ) relative to TMS (0.00). IR spectra were taken on a Perkin-Elmer 298 spectrophotometer in $CHCl_3$ or neat as indicated. M.ps were determined on a Fischer–Johns hot-stage m.p.

Table 3. Reaction of sodium N-(*E*)-4,6-heptadienyl succinamate in water with dienophiles[a]

Dienophile	Time/h	Product(s)[b]	Yield %[c]
	6	 25	89
	3	 CIS : TRANS 1 : 1.5	81
	10	 26	56
Methyl vinyl ketone	22	 27	72
Acrolein	15	 1:1	81
Methacrolein	15	 28	79

[a] All reactions were carried out 2.0 M in diene at 25°C. A five-fold excess of diene was employed. [b] All products were characterized as their methyl esters. [c] Yields reported are for chromatographically pure materials.

apparatus and are uncorrected. Exact mass determinations were performed on a Kratos high-resolution mass spectrometer (MS 80/RFA). E. Merck silica gel No. 7734 (70–230 mesh) was used for column chromatography and E. Merck silica gel No. 9385 (230–400 mesh), for flash chromatography. Radial chromatography was carried out on a Chromatotron Model 7924 using a 2 mm plate. E. Merck precoated silica gel plates (0.25 mm thickness) were used for analytical TLC. Preparative TLC was performed on E. Merck precoated silica gel plates (0.5 and 2 mm thickness). All reagents were freshly distilled, sublimed or recrystallized. All solvents were reagent grade and anhydrous solvents were dried prior to use. Hexamethylphosphoramide, pyridine and triethylamine were distilled from calcium hydride; Et_2O and THF were distilled from benzophenone ketyl; CH_2Cl_2 and Ac_2O were distilled from P_2O_5, and toluene was distilled from Na.

(*E*)-*2,4-Pentadienyl amine* (**7**). To a soln of 34.1 g (0.23 mol) of (*E*)-**10**[3] in 250 ml of DMSO under Ar at ambient temp was added 22.6 g (0.35 mol) of sodium azide. After 17 h, the mixture was diluted with H_2O and extracted four times with Et_2O. The combined Et_2O extracts were washed with H_2O and dried ($MgSO_4$). Filtration and evaporation of the solvent *in vacuo* afforded 25.3 g (100%) of crude azide [IR (neat) 2090 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.40 (m, 2H), 5.80 (m, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 3.83 (d, 2H, J = 6 Hz)] which was used directly in the next reaction.

To a suspension of 7.0 g (0.18 mol) of $LiAlH_4$ in 300 ml of anhydrous Et_2O cooled to 0° was added dropwise 25.0 g (0.23 mol) of the above azide. After 1 h, the reaction was quenched with 7.0 ml of H_2O and 7.0 ml of 15% NaOH aq followed by an additional 21 ml of H_2O.

The Et_2O layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure, leaving crude amine. Purification by distillation provided 12.03 g (65%) of **7** as a colorless liquid, b.p. 43–45°, 40 mmHg: IR (neat) 3360, 3280, 3200, 3080, 3030, 3005, 2970, 2910, 2850, 1660, 1605, 1450, 1415, 1380, 1340, 1305, 1105, 1010, 960, 905, 860, 760, cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.27 (dt, 1H, J = 17, 10 Hz), 6.09 (dd, 1H, J = 15, 10 Hz), 5.74 (dt, 1H, J = 15, 6 Hz), 5.10 (d, 1H, J = 17 Hz), 4.97 (d, 1H, J = 10 Hz), 3.27 (d, 2H, J = 6 Hz), 1.43 (br s, 2H); MS: M^+ 83.0745 (calc for C_5H_9N: 83.0735).

(*E*)-*3,5-Hexadienyl amine* (**8**). To a soln of 5.0 g (21 mmol) of (*E*)-**11**[4] in 25.0 ml of DMSO was added 2.0 g (31 mmol) of sodium azide. After 18 h at ambient temp the mixture was diluted with H_2O and the product was extracted with Et_2O. The combined Et_2O extracts were washed with H_2O and dried ($MgSO_4$). Concentration under reduced pressure afforded 2.2 g (88%) of crude azide [IR (neat) 2000 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 6.33 (dt, 1H, J = 16, 9 Hz), 6.13 (dd, 1H, J = 14, 10 Hz), 5.63 (dt, 1H, J = 15, 6 Hz), 5.16 (d, 1H, J = 12 Hz), 5.03 (d, 1H, J = 6 Hz), 3.33 (t, 2H, J = 6 Hz), 2.40 (q, 2H, J = 6 Hz)] which was used directly in the next reaction.

To a suspension of 695 mg (18.3 mmol) of $LiAlH_4$ in 250 ml of Et_2O cooled to 0° was added dropwise 2.2 g (18.3 mmol) of the above azide over 15 min. After 30 min at 0°, the reaction was warmed to ambient temp. Stirring was continued for 30 min. The reaction was quenched with 0.7 ml of H_2O and 0.7 ml of 5% NaOH aq followed by an additional 2.1 ml of H_2O. The Et_2O layer was dried ($MgSO_4$). The solvent was removed under reduced pressure, leaving crude amine. Purification by distillation afforded 1.39 g (78%) of pure **8**, b.p. 44–45°, 10 mmHg: IR (neat) 3370, 3290, 3080, 3030, 3000, 2920, 2850, 1650, 1608, 1440, 1420, 1010, 950, 900 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.24 (dt, 1H, J = 17, 10 Hz), 6.03 (dd, 1H, J = 15, 10 Hz), 5.58 (dt, 1H, J = 15, 7 Hz), 5.04 (d, 1H, J = 17 Hz), 4.91 (d, 1H, J = 10 Hz), 2.68 (t, 2H, 7 Hz), 2.15 (q, 2H, J = 7 Hz), 1.19 (br s, 2H); MS: M$^+$ 97.0897 (calc for $C_6H_{11}N$: 97.0891).

(*E*)-4,6-*Heptadienyl amine* (**9**). To a soln of 10.0 g (42 mmol) of tosylate **11** in 125 ml of DMSO was added 3.1 g (63 mmol) of sodium cyanide. After stirring at ambient temp for 16 h, the mixture was diluted with H_2O. The product was isolated by extraction with Et_2O. The combined Et_2O extracts were washed with H_2O and dried ($MgSO_4$). Concentration under reduced pressure gave 4.1 g (92%) of nitrile [IR (neat) 2245 cm^{-1}; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 6.42 (dt, 1H, J = 16, 10 Hz), 6.32 (dd, 1H, J = 15, 10 Hz), 5.71 (dt, 1H, J = 15, 7 Hz), 5.18 (d, 1H, J = 15 Hz), 5.07 (d, 1H, J = 10 Hz), 2.41 (s, 4H)] which was used directly in the next reaction.

The above nitrile (4.0 g, 37.3 mmol) was added dropwise over 30 min to a suspension of 1.1 g (28.0 mmol) of $LiAlH_4$ in 50 ml of Et_2O cooled to 0°. After 2 h at 0°, the reaction was quenched with 6.0 ml of H_2O and 6.0 ml of 15% NaOH aq followed by an additional 18.0 ml of H_2O. After warming to room temp, anhyd $MgSO_4$ was added and the entire contents of the flask were filtered. The solvent was removed *in vacuo*, leaving crude amine. Purification by distillation provided 3.19 g (77%) of **9**, b.p. 52–53°, 4 mmHg: IR (neat) 3360, 3270, 3080, 3030, 3000, 2920, 2865, 1801, 1650, 1601, 1440, 1008, 995, 901 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.24 (dt, 1H, J = 17, 10 Hz), 6.00 (dd, 1H, J = 15, 10 Hz), 5.63 (dt, 1H, J = 15, 7 Hz), 5.02 (d, 1H, J = 15 Hz), 4.89 (d, 1H, J = 10 Hz), 2.63 (t, 2H, J = 7 Hz), 2.06 (q, 2H, J = 7 Hz), 1.48 (p, 2H, J = 7 Hz), 1.06 (s, 2H); MS: M$^+$ 111.1040 (calc for $C_7H_{13}N$: 111.1048).

General procedure for the cyclocondensation of dienyl ammonium chlorides with dienophiles. To a soln of the amine (0.74 mmol) in 0.20 ml of H_2O at 0° was added 0.13 ml of 5.0 M HCl. After warming to ambient temp, the dienophile (0.15 mmol) was added to the colorless, homogeneous aqueous soln of dienyl amine hydrochloride and stirred vigorously. The reactions were monitored by TLC. Upon completion of the reaction, the mixture was diluted with H_2O and neutralized with $NaHCO_3$. The product was isolated by extraction with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$). Concentration under reduced pressure afforded the crude Diels–Alder adduct.

Diels–Alder adduct **12**. Reaction of an aq soln of (*E*)-2,4-pentadienyl ammonium chloride, prepared from 61 mg (0.74 mmol) of (*E*)-2,4-pentadienyl amine in 0.22 ml of H_2O and 0.15 ml of 5.0 M HCl, with 20 mg (0.15 mmol) of 2,6-dimethylbenzoquinone at 25° for 32 h according to the general procedure gave 29 mg (98%) of **12**, which was homogeneous by TLC: R_f 0.46 (EtOAc–hexane, 1:1); IR ($CHCl_3$) 3030, 2960, 2920, 2850, 1670, 1625, 1596, 1440, 1395, 1375, 1335, 1295, 1245, 1205, 1140, 1000, 975, 905, 880 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.66 (dddd, 1H, J = 10, 6, 2.5, 2.5 Hz), 5.54 (dt, 1H, J = 10, 3 Hz), 4.19 (dd, 1H, J = 17, 7.5 Hz), 3.92 (dd, 1H, J = 17, 1 Hz), 2.57 (dd, 1H, J = 11, 6 Hz), 2.50 (m, 1H), 2.17 (dt, 1H, J = 17, 6 Hz), 2.11 (s, 3H), 1.89 (dddd, 1H, J = 17, 11, 5, 2.5 Hz), 1.17 (s, 3); MS: M$^+$ 201.1157 (calc for $C_{13}H_{15}NO$: 201.1154).

Diels–Alder adduct **13**. Reaction of an aq soln of (*E*)-2,4-pentadienyl ammonium chloride, prepared from 91.5 mg (1.10 mmol) of (*E*)-2,4-pentadienyl amine in 0.33 ml of H_2O and 0.22 ml of 5.0 M HCl, with 30 mg (0.22 mmol) of 2,5-dimethylbenzoquinone at 25° for 120 h according to the general procedure gave 38 mg (86%) of **13**, which was homogeneous by TLC: R_f 0.46 (EtOAc–hexane, 1:1); IR ($CHCl_3$) 3020, 2960, 2920, 2850, 1675, 1625, 1595, 1435, 1375, 1355, 1335, 1320, 1305, 1290, 1245, 1205, 1165, 1140, 1090, 1005, 975, 945, 905, 885 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.93 (s, 1H), 5.64 (dddd, 1H, J = 10, 6, 2, 2 Hz), 5.54 (dt, 1H, J = 10, 3 Hz), 4.17 (dd, 1H, J = 17, 7 Hz), 3.86 (d, 1H, J = 17 Hz), 2.64 (dd, 1H, J = 12, 6 Hz), 2.47 (m, 1H), 2.12 (dt, 1H, J = 17, 6 Hz), 1.92 (s, 3H), 1.90 (m, 1H), 1.16 (s, 3H); MS: M$^+$ 201.1153 (calc for $C_{13}H_{15}NO$: 201.1154).

Diels–Alder adduct **14**. Reaction of an aq soln of (*E*)-2,4-pentadienyl ammonium chloride, prepared from 54.6 mg (0.66 mmol) of (*E*)-2,4-pentadienyl amine in 0.22 ml of H_2O and 0.15 ml of 5.0 M HCl, with 20 mg (0.13 mmol) of 2-methoxy-2-methylbenzoquinone at 25° for 20 h gave 27.2 mg (95%) of adduct **14**, which was homogeneous by TLC: R_f 0.19 (EtOAc–hexane, 4:1); IR ($CHCl_3$) 3040, 3010, 2980, 2950, 2870, 1660, 1620, 1590, 1465, 1450, 1405, 1380, 1355, 1340, 1305, 1230, 1220, 1208, 1180, 1115, 1090, 1085, 990, 970, 910, 850 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.67 (dddd, 1H, J = 10, 6, 2, 2 Hz), 5.55 (dt, 1H, J = 10, 3 Hz), 5.53 (s, 1H), 4.24 (dd, 1H, J = 17, 7 Hz), 3.99 (dd, 1H, J = 17, 1 Hz), 3.80 (s, 3H), 2.58 (dd, 1H, J = 12, 6 Hz), 2.56 (m, 1H), 2.23 (dt, 1H, J = 17, 6 Hz), 1.93 (dddd, 1H, J = 17, 12, 5, 2 Hz), 1.24 (s, 3H); MS: M$^+$ 217.1089 (calc for $C_{13}H_{15}NO_2$: 217.1103).

Diels–Alder adduct **16**. Reaction of an aq soln of (*E*)-2,4-pentadienyl ammonium chloride, prepared from 67 mg (0.81 mmol) of (*E*)-2,4-pentadienyl amine in 0.24 ml of H_2O and 0.16 ml of 5.0 M HCl, with 25 mg (0.16 mmol) of **15** at 25° for 23 h gave 26 mg (78%) of crystalline lactam **16**, m.p. 201–202°: IR ($CHCl_3$) 3430, 3210, 3025, 2990, 2960, 2940, 2880, 2840, 1695, 1485, 1460, 1440, 1420, 1300, 1290, 1275, 1235, 1210, 1160, 1070, 1055, 1030, 1020, 985, 972, 930, 905, 895, 810 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.95 (dddd, 1H, J = 10, 7, 3, 3 Hz), 5.82 (br s, 1H), 5.58 (ddd, 1H, J = 10, 4, 2 Hz), 4.41 (d, 1H, J = 5 Hz), 4.24 (t, 1H, J = 3 Hz), 3.68 (dd, 1H, J = 10, 6 Hz), 3.19 (dd, 1H, J = 10, 2 Hz), 2.69 (dd, 1H, J = 5, 3 Hz), 2.38 (dt, 1H, J = 15, 7 Hz), 2.21 (dd, 1H, J = 10, 7 Hz), 2.01 (ddd, 1H, J = 16, 12, 7 Hz), 1.84 (ddd, 1H, J = 13, 6, 3 Hz), 1.77 (ddd, 1H, J = 11, 5, 3 Hz), 1.64 (br s, 1H), 1.58 (dd, 1H, J = 11, 5 Hz); MS: M$^+$ 205.1098 (calc for $C_{12}H_{15}NO_2$: 205.1103).

Diels–Alder adduct **17**. Reaction of an aq soln of (*E*)-3,5-hexadienyl ammonium chloride, prepared from 71.3 mg (0.74 mmol) of (*E*)-3,5-hexadienyl amine in 0.22 ml of H_2O and 0.15 ml of 5.0 M HCl, with 23 mg (0.17 mmol) of 2,5-dimethylbenzoquinone at 25° for 2 h provided after workup 31.2 mg (99%) of **17**, which was homogeneous by TLC analysis: R_f 0.31 (EtOAc–hexane, 4:1); IR ($CHCl_3$) 3030, 3010, 2970, 2940, 2855, 1675, 1660, 1635, 1615, 1440, 1380, 1358, 1309, 1285, 1260, 1240, 1210, 1175, 1080, 1055, 1010, 955, 925, 870 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.75 (dddd, 1H, J = 10, 6, 2, 2 Hz), 5.56 (m, 1H), 4.08 (ddd, 1H, J = 17, 4, 2 Hz), 3.54 (ddd, 1H, J = 17, 12, 3 Hz), 2.60 (dd, 1H, J = 11, 5 Hz), 2.43 (dt, 1H, J = 19, 5 Hz), 2.10 (s, 3H), 2.10 (m, 1H), 2.03 (m, 1H), 1.81 (m, 1H), 1.25 (m, 1H), 1.10 (s, 3H); MS: M$^+$ 215.1310 (calc for $C_{14}H_{17}NO$: 215.1310).

Diels–Alder adduct **18**. Reaction of an aq soln of (*E*)-3,5-hexadienyl ammonium chloride, prepared from 86.7 mg (0.89 mmol) of (*E*)-3,5-hexadienyl amine in 0.25 ml of H_2O and 0.18 ml of 5.0 M HCl, with 23 mg (0.17 mmol) of 2,5-dimethylbenzoquinone at 25^c for 21 h afforded crude adduct which was purified on 10 g of silica gel. Elution with Me_2CO–CH_2Cl_2 (1:9) afforded 28 mg (77%) of pure crystalline **18**, m.p. 88–89^c: R_f 0.31 (EtOAc–hexane, 4:1); IR (neat) 3020, 2970, 2930, 2870, 2850, 1680, 1618, 1440, 1380, 1345, 1285, 1235, 1215, 1190, 1160, 1110, 1095, 1080, 1050, 1040, 1020, 1000, 980, 935, 905, 870 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.61 (s, 1H), 5.76 (m, 1H), 5.46 (m, 1H), 3.93 (dd, 1H, J = 12, 5 Hz), 3.48 (ddd, 1H, J = 12, 6, 2 Hz), 2.59 (dd, 1H, J = 12, 6 Hz), 2.27 (m, 1H), 2.14 (m, 1H), 1.98 (m, 2H), 1.88 (s, 3H), 1.54 (m, 1H), 1.30 (s, 3H); MS: M$^+$ 215.1312 (calc for $C_{14}H_{17}NO$: 215.1310).

Diels–Alder adduct **19**. Reaction of an aq soln of (*E*)-3,5-hexadienyl ammonium chloride, prepared from 76.5 mg (0.79 mmol) of (*E*)-3,5-hexadienyl amine in 0.23 ml of H_2O and 0.16 ml of 5.0 M HCl, with 23.4 mg (0.15 mmol) of 2-methoxy-6-methylbenzoquinone at 25° for 1.75 h gave a quantitative yield of crude adduct, which was purified on 10 g of silica gel. Elution with Me_2CO–CH_2Cl_2 (1:3) provided 35.0 mg (98%) of pure crystalline **19**, m.p. 88.5–90.0°: IR (CCl_4) 3025, 2975, 2930, 2870, 2850, 1660, 1595, 1460, 1440, 1385, 1370, 1345, 1318, 1280, 1265, 1225, 1180, 1115, 1095, 1065, 1015, 970, 840 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.46 (s, 1H), 5.42 (d, 1H, J = 10 Hz), 4.02 (dd, 1H, J = 19, 5 Hz), 3.76 (s, 3H), 3.59 (ddd, 1H, J = 19, 12, 5 Hz), 2.53 (dd, 1H, J = 11, 6 Hz), 2.32 (br s, 1H), 2.23 (m, 1H), 1.9–2.1 (m, 2H), 1.59 (dt, 1H, J = 14, 4 Hz), 1.14 (s, 3H); MS: M^+ 231.1256 (calc for $C_{14}H_{17}NO_2$: 231.1259).

Diels–Alder adduct **22**. To a suspension of 164 mg (1.48 mmol) of (*E*)-**9** in 0.42 ml of H_2O at ambient temp was added 0.32 ml of 4.61 M HCl followed by the addition of 41 mg (0.30 mmol) of 2,5-dimethylbenzoquinone. The heterogeneous mixture became homogeneous after 8 h. TLC analysis (30% EtOAc–hexane) after 11 h indicated complete consumption of starting benzoquinone. The reaction was quenched with excess solid $NaHCO_3$ and diluted with 10 ml of H_2O. The product was isolated by extraction with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the filtrate was concentrated *in vacuo*, leaving 105 mg of crude amine which was immediately subjected to acetylation.

A soln of the above amine in 8 ml of CH_2Cl_2 was treated with 0.14 ml (1.50 mmol) of Ac_2O and 0.35 ml of Et_3N. The reaction was quenched after 2 h by pouring the contents of the reaction flask into 20 ml of 2% HCl aq. The product was isolated by extraction with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by radial preparative liquid chromatography (chromatotron) using a 2 mm thick silica gel plate. Elution with EtOAc provided 54.2 mg (62%) of pure **22**: IR ($CHCl_3$) 3425, 3360, 3000, 2975, 2940, 2920, 2900, 2840, 1655, 1615, 1510, 1422, 1365, 1325, 1260, 1200, 1144, 1121, 1095, 1020, 990, 875 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.45 (q, 1H, J = 1.5 Hz), 5.79 (m, 2H), 5.69 (m, 1H), 3.35 (m, 1H), 3.19 (m, 1H), 3.08 (dd, 1H, J = 9, 7 Hz), 2.3–2.4 (m, 2H), 2.01 (d, 3H, J = 1.5 Hz), 1.99 (s, 3H), 1.5–1.7 (m, 4H), 1.10 (s, 3H); MS: M^+ 289.1689 (calc for $C_{17}H_{23}NO_3$: 289.1678).

N-(*E*)-4,6-*Heptadienyl succinamic acid* (**23**). To a soln of 758 mg (6.82 mmol) of (*E*)-4,6-heptadienyl amine in 130 ml of CH_2Cl_2 were added 1.4 g (14.0 mmol) of succinic anhydride and 86 mg (0.70 mmol) of 4-dimethylaminopyridine. After stirring for 24 h the mixture was extracted three times with sat $NaHCO_3$ aq and the combined aq layers were acidified with H_2SO_4. The product was isolated by extraction with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure, leaving 1.1 g (75%) of **23** as a white crystalline material, m.p. 87.5–89.5°: R_f 0.42 (EtOAc–hexane–HOAc, 7:2:1); IR (KBr) 3310, 2300–3500 (broad), 1695, 1650, 1555, 1425, 1340, 1300, 1285, 1205, 1005, 970, 960, 950, 940, 910, 800 cm^{-1}; ^{1}H-NMR (360 MHz, CD_3OD) δ 6.33 (dt, 1H, J = 16.6, 10.5 Hz), 6.11 (dd, 1H, J = 15.2, 10.5 Hz), 5.72 (dt, 1H, J = 15.2, 6.8 Hz), 5.10 (d, 1H, J = 15.2 Hz), 4.97 (d, 1H, J = 10.5 Hz), 3.35 (br s, 1H), 3.20 (t, 2H, J = 6.8 Hz), 2.62 (t, 2H, 6.8 Hz), 2.49 (t, 2H, 6.8 Hz), 2.15 (q, 2H, 6.8 Hz), 1.62 (p, 2H, J = 6.8 Hz); MS: M^+ 211.1217 (calc for $C_{11}H_{17}NO_3$: 211.1208).

General procedure for the cyclocondensation of sodium N-(*E*)-4,6-*heptadienyl succinamate with dienophiles*. To a suspension of N-(*E*)-4,6-heptadienyl succinamic acid (1.10 mmol) in 0.55 ml of H_2O was added solid $NaHCO_3$ (1.05 mmol) portionwise. After gas evolution was complete, the dienophile (0.22 mmol) was added to the colorless soln. Reactions were monitored by TLC. Upon completion of the reaction, the mixture was diluted with H_2O, acidified with 10% HCl and the product isolated by extraction with CH_2Cl_2. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude acid esterified with an ethereal soln of diazomethane.

Diels–Alder adduct **25**. Reaction of an aq soln of sodium N-(*E*)-4,6-heptadienyl succinamate, prepared from 206 mg (0.97 mmol) of N-(*E*)-4,6-heptadienyl succinamic acid suspended in 0.49 ml of H_2O and 78 mg (0.92 mmol) of solid $NaHCO_3$, with 30 mg (0.20 mmol) of 2-carbomethoxy-7-oxabicyclo[2.2.1]-hept-2-ene at 25° for 6 h gave, after esterification with ethereal diazomethane, crude Diels–Alder adduct, which was purified on 40 g of silica gel. Elution with EtOAc–hexane (7:3) afforded 66 mg (89%) of pure **25** as a colorless, viscous oil: R_f 0.25 (EtOAc–hexane, 3:2); IR ($CHCl_3$) 3430, 3010, 2960, 2930, 2840, 1715, 1660, 1505, 1430, 1350, 1310, 1280, 1220, 1185, 1150, 1115, 1070, 1040, 1020, 980, 925, 895 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 5.99 (br s, 1H), 5.88 (m, 1H), 5.48 (m, 1H), 4.37 (d, 1H, J = 5 Hz), 4.14 (d, 1H, J = 5 Hz), 3.62 (s, 3H), 3.58 (s, 3H), 3.21 (m, 1H), 2.61 (t, 2H, J = 6 Hz), 2.41 (t, 2H, J = 6 Hz), 2.34 (m, 1H), 2.24 (t, 1H, J = 10 Hz), 2.15 (br d, 1H, J = 11 Hz), 1.5–1.9 (m, 5H), 1.42 (m, 2H), 1.20 (m, 1H), 1.07 (m, 1H).

Diels–Alder adduct **26**. Reaction of an aq soln of sodium N-(*E*)-4,6-heptadienyl succinamate, prepared from 233 mg (1.10 mmol) of N-(*E*)-4,6-heptadienyl succinamic acid in 0.55 ml of H_2O and 88 mg (1.05 mmol) of solid $NaHCO_3$, with 30 mg of 2,5-dimethylbenzoquinone at 25° for 10 h provided, after esterification with ethereal diazomethane, crude ester **26**, which was purified on 40 g of silica gel. Elution with EtOAc–hexane (1:1) afforded 45 mg (56%) of pure **26**: R_f 0.35 (EtOAc–hexane, 7:3); IR ($CHCl_3$) 3500, 3435, 3360, 3020, 2980, 2940, 2920, 2850, 1725, 1660, 1620, 1510, 1430, 1370, 1360, 1320, 1265, 1220, 1200, 1160, 1125, 1075, 990, 900, 880 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.42 (q, 1H, J = 1.4 Hz), 6.04 (m, 1H), 5.76 (m, 1H), 5.65 (m, 1H), 3.64 (s, 3H), 3.31 (m, 1H), 3.16 (m, 1H), 3.06 (dd, 1H, J = 9, 7 Hz), 2.63 (t, 2H, J = 7 Hz), 2.45 (t, 2H, J = 7 Hz), 2.2–2.4 (m, 3H), 1.98 (s, 3H), 1.4–1.7 (m, 4H), 1.07 (s, 3H); MS: M^+ 377.1819 (calc for $C_{20}H_{17}NO_6$: 377.1838).

Diels–Alder adduct **27**. Reaction of an aq soln of sodium N-(*E*)-4,6-heptadienyl succinamate, prepared from 301 mg (1.43 mmol) of N-(*E*)-4,6-heptadienyl succinamic acid suspended in 0.71 ml of H_2O and 120 mg (1.43 mmol) of $NaHCO_3$, with 20 mg (0.29 mmol) of methyl vinyl ketone at 25° for 22 h gave, after esterification with ethereal diazomethane, crude Diels–Alder adduct, which was purified by radial preparative liquid chromatography (chromatotron) using a 2 mm thick silica gel plate. Elution with EtOAc–hexane (7:3) provided 60.4 mg (72%) of pure **27**: IR ($CHCl_3$) 3440, 3380, 3020, 2990, 2930, 2860, 2830, 1730, 1700, 1665, 1515, 1450, 1435, 1410, 1350, 1320, 1295, 1265, 1230, 1205, 1165, 1080, 990, 905, 840 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 6.07 (m, 1H), 5.70 (m, 1H), 5.64 (m, 1H), 3.61 (s, 3H), 3.13 (m, 2H), 2.66 (m, 1H), 2.58 (t, 2H, J = 7 Hz), 2.47 (m, 1H), 2.39 (t, 2H, J = 7 Hz), 2.09 (s, 3H), 1.0–2.0 (m, 9H); MS: M^+ 295.1784 (calc for $C_{16}H_{25}NO_4$: 295.1784).

Diels–Alder adduct **28**. Reaction of an aq soln of sodium N-(*E*)-4,6-heptadienyl succinamate, prepared from 226 mg (1.07 mmol) of N-(*E*)-4,6-heptadienyl succinamic acid suspended in 0.54 ml of H_2O and 90 mg (1.07 mmol) of solid $NaHCO_3$, with 15 mg (0.21 mmol) of methacrolein at 25° for 15 h gave, after esterification with ethereal diazomethane, crude adduct **28**, which was purified on 50 g of silica gel. Elution with EtOAc–hexane (1:1) provided 50 mg (79%) of pure **28** as a colorless oil: R_f 0.18 (EtOAc–hexane, 7:3); IR ($CHCl_3$) 3435, 3400, 3010, 2990, 2850, 2700, 1715, 1660, 1515, 1455, 1435, 1410, 1360, 1320, 1230, 1200, 1160, 1080, 1040, 990, 905, 840 cm^{-1}; ^{1}H-NMR (360 MHz, $CDCl_3$) δ 9.59 (s, 1H), 5.94 (m, 1H), 5.68 (m, 2H), 3.65 (s, 3H), 3.19 (m, 2H), 2.63 (t, 2H, J = 6 Hz), 2.42 (t, 2H, J = 6 Hz), 2.04 (m, 3H), 1.78 (dt, 1H, J = 14, 7 Hz), 1.64 (m, 1H), 1.47 (m, 3H), 1.21 (m, 1H), 1.05 (s, 3H); MS: M^+ 295.1787 (calc for $C_{16}H_{25}NO_4$: 295.1784).

Acknowledgements—This investigation was supported by a Public Health Service Research Grant (GM 33605) from the National Institute of General Medical Sciences and the NSERC of Canada for a graduate fellowship to P.G. The 360 MHz NMR instrument (Nicolet) and Kratos high-resolution mass spectrometer (MS 80/RFA), used in the above studies, were purchased in part through funds provided by the National Sciences Foundation (Grants Nos. CHE-81-05004 and CHE-81-11957, respectively).

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