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Intramolecular Diels–Alder Reactions. 10. Syntheses and Cyclizations of Some *N*-(Cinnamyl and phenylpropargyl)cinnamamides and Phenylpropiolamides[1a]

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The nine possible unsaturated amides $Ph(C_2)CH_2NHC(=O)(C_2)'Ph$, where (C_2) and $(C_2)'$ are variously *cis*-CH=CH–, *trans*-CH=CH–, and –C≡C– groups, were synthesized. Diynic amide **6** underwent intramolecular Diels–Alder reaction in refluxing Ac_2O to form a mixture of benz[*f*]isoindoles **15a** (from cyclization in mode 1) and **16a** (from cyclization in mode 2). Under these same conditions *trans,trans*-dienic amide **8** did not cyclize, while four other amides gave cyclization in only one mode (for each) to form hydro derivatives of **15a** and **16a**. Modal selectivity in the cyclizations is interpreted in terms of relative frontier molecular orbital energy levels for the various substrate molecules.

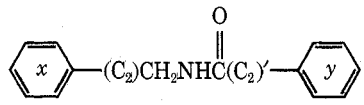
In a series of preceding papers from this laboratory[2-6] we presented the syntheses and intramolecular Diels–Alder reactions (by means of refluxing acetic anhydride) of unsaturated esters of the $Ar(C_2)CH_2OC(=O)(C_2)'Ar'$ type, where Ar and Ar′ are phenyl or substituted phenyl groups and (C_2) and $(C_2)'$ are variously –C≡C–, *cis*-CH=CH–, and *trans*-CH=CH– groups. Of the nine possible combinations for (C_2) and $(C_2)'$ only five types have thus far been synthesized, and just three of these types have been found susceptible to intramolecular Diels–Alder reaction. Successful cyclizations led to the formation of cyclolignan lactones, compounds which bear the skeletal structure of 4- (or 9-) arylnaphtho[2,3-*c*]-furan-1(3*H*)-one. An extension of these studies to the syntheses and cyclizations of the analogous amides $Ph(C_2)$-$CH_2NRC(=O)(C_2)'Ph$, where R = H or benzyl, is underway in our laboratory. Studies on four *N*-benzyl amides have already been reported,[7] while the present paper describes the syntheses of all nine possible parent amides (R = H) and studies on cyclizations of six of them. Cyclization of a seventh parent amide will be considered in a subsequent paper.[8]

Used in the syntheses of the unsaturated amides were the hydrochloride salts of *trans*-cinnamylamine (**1**),[9] phenylpropargylamine (**2**), and *cis*-cinnamylamine (**3**). Amine salt **2** was obtained in 79% overall yield by Gabriel synthesis from phenylpropargyl chloride.[10] Low-pressure catalytic hydrogenation of **2** in the presence of Pd–$BaSO_4$–quinoline gave nearly a quantitative yield of **3**. Schotten–Baumann condensations between these amine salts and the freshly prepared acid chlorides from phenylpropiolic acid, *trans*-cinnamic acid, and *cis*-cinnamic acid produced the nine crystalline amides **4–12**, in yields of 57–81% (Table I). *N*-(*cis*-Cinnamyl)-*trans*-cinnamamide (**7**) was also obtained (55%) by hydrogenation of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) in the presence of Lindlar catalyst plus quinoline.

Of special interest in the syntheses of **10–12** is the handling of *cis*-cinnamic acid. Saponification of ethyl *cis*-cinnamate[11] gave *cis*-cinnamic acid, which could be stored in dry benzene at 0–10 °C in the dark for several months without isomerization. Just before use, the acid was converted into its sodium salt by means of sodium hydride, and then into *cis*-cinnamoyl chloride (in high isomeric purity) by means of thionyl chloride.

Identities of the amides were checked by ultraviolet, ^1H NMR, and infrared spectra (as well as by elemental analyses). In particular, absorption bands were found for N–H stretching at ca. 3440 cm^{-1} (weak) and for the carbonyl moiety of an N-substituted amide at 1650–1670 cm^{-1} (strong) in all compounds.[12a] Bands for the trans-disubstituted alkene linkage[12b] at ca. 970 cm^{-1} and for the triple bond in the acid moiety[12c] at 2220 cm^{-1} were also appropriately observed.

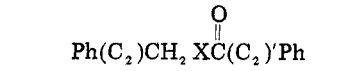
Table I



Registry no.	Compd	(C_2) unit	$(C_2)'$ unit	Yield,[a] %	Mp,[b] °C
59015-31-5	4	*cis*-CH=CH–	–C≡C–	61	101.5–102.5[c]
59015-32-6	5	*trans*-CH=CH–	–C≡C–	80	111–112[d]
59015-33-7	6	–C≡C–	–C≡C–	66	123.5–124.5[e]
59015-35-9	7	*cis*-CH=CH–	*trans*-CH=CH–	79	137–138[d]
59015-34-8	8	*trans*-CH=CH–	*trans*-CH=CH–	81	129–130[e]
59015-36-0	9	–C≡C–	*trans*-CH=CH–	59	142–143[e]
59015-37-1	10	*cis*-CH=CH–	*cis*-CH=CH–	58	62–63[c]
59015-38-2	11[f]	*trans*-CH=CH–	*cis*-CH=CH–	72	64.5–65.5[c]
59015-39-3	12	–C≡C–	*cis*-CH=CH–	57	96.5–97.5[c]

[a] Of amide product (from Schotten–Baumann reaction) after one crystallization from solvent. [b] For analytically pure product. [c] Recrystallized from benzene–petroleum ether (bp 60–90 °C). [d] Recrystallized from aqueous ethanol. [e] Recrystallized from ethanol. [f] This compound was chromatographed (silica gel–$CHCl_3$) before crystallization.

Table II. Comparison of [4 + 2] Cycloaddition Products from Unsaturated Amides and Esters in Refluxing Acetic Anhydride

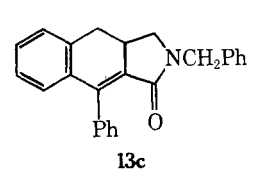


(C_2) unit	$(C_2)'$ unit	X[a]	Isolated cyclization product(s): Formula(s)	Total Yield, %	Mode(s) of cyclization
trans-CH=CH–	*trans*-CH=CH–	O,[5] NH, NCH_2Ph[7]		None[b]	None[b]
trans-CH=CH–	–C≡C–	O[5]	17	46[c]	1
		NH	13a	74	1
		NCH_2Ph[7]	13c	100	1
trans-CH=CH–	*cis*-CH=CH–	O[2]	27[d]	(20)	(1)
		NH	26	25	2
–C≡C–	*trans*-CH=CH–	O[5]		None[b]	None[b]
		NH	14a, 16a	75	2
		NCH_2Ph[7]	16c, 22c	17	2
–C≡C–	–C≡C–	O[5]	18	39	1 (and 2)[e]
		NH	15a, 16a	72[f]	1 and 2
		NCH_2Ph[7]	15c	14	1
–C≡C–	*cis*-CH=CH–	NH	14a, 16a[g]	23	2
cis-CH=CH–	–C≡C–	NH	13a	32	1

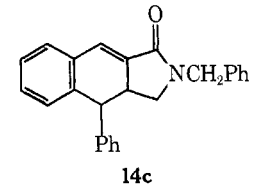
[a] Reference numbers are those given at the end of this paper. [b] Cyclization did not occur. [c] Overall yield from phenylpropiolic acid. [d] Reaction has been tried only with substituted phenyl groups. [e] Only mode 1 product was obtained with unsubstituted phenyl groups. Substituted phenyl groups gave mixtures of products from both modes 1 and 2.[4] [f] Ratio of 15a:16a 1.3:1. [g] Plus [2 + 2] cycloaddition product.

Solutions of amides **4–6, 8, 9** and **11** in acetic anhydride (usually under high-dilution conditions of 1 g of amide per 250–1250 ml of solvent) were refluxed for 4–7 h and processed further for isolation of products. *N*-(*trans*-Cinnamyl)-*trans*-cinnamamide (**8**) formed a red, viscous liquid, believed to contain only polymeric materials (as based on TLC and ^1H NMR analyses). Failure of *N*-benzyl-*N*-(*trans*-cinnamyl)-*trans*-cinnamamide[7] and of *trans*-cinnamyl-*trans*-cinnamate[5] (plus a number of its ring-substituted derivatives)[4] to undergo cyclization under these conditions has been noted previously. The nonreactivity toward intramolecular Diels–Alder cyclization of all of these trans,trans dienic compounds may be ascribed to steric hindrance to the attainment of the geometry required in the transition state.[4]

In contrast, each of the other five amides formed a crystalline intramolecular cycloaddition product of the Diels–Alder type. It should be noted, however, that two modes of intramolecular Diels–Alder reaction are possible. Mode 1 involves action of the $(C_2)'$ unit of the acid moiety as a "dienophile" and of the $Ph(C_2)$ unit of the amine moiety as a "diene". Cyclization thereby occurs into the phenyl ring of the amine moiety (ring *x*) in the manner expected for a normal Diels–Alder reaction. Alternatively, mode 2 involves action of the (C_2) unit of the amine moiety as a "dienophile" and of the $Ph(C_2)'$ unit of the acid moiety as a "diene". Cyclization in this mode occurs into the phenyl ring of the acid moiety (ring *y*) in an "abnormal" Diels–Alder manner. Both modes of cyclization were found in this study. They are distinguished by structural investigation of the product(s) formed—in particular by transformation (where necessary) into the reference compounds **15** and **16**, respectively. Scheme I summarizes these transformations. Table II gives yields of the N-acetylated products formed (from X = NH), the mode(s) of cycli-

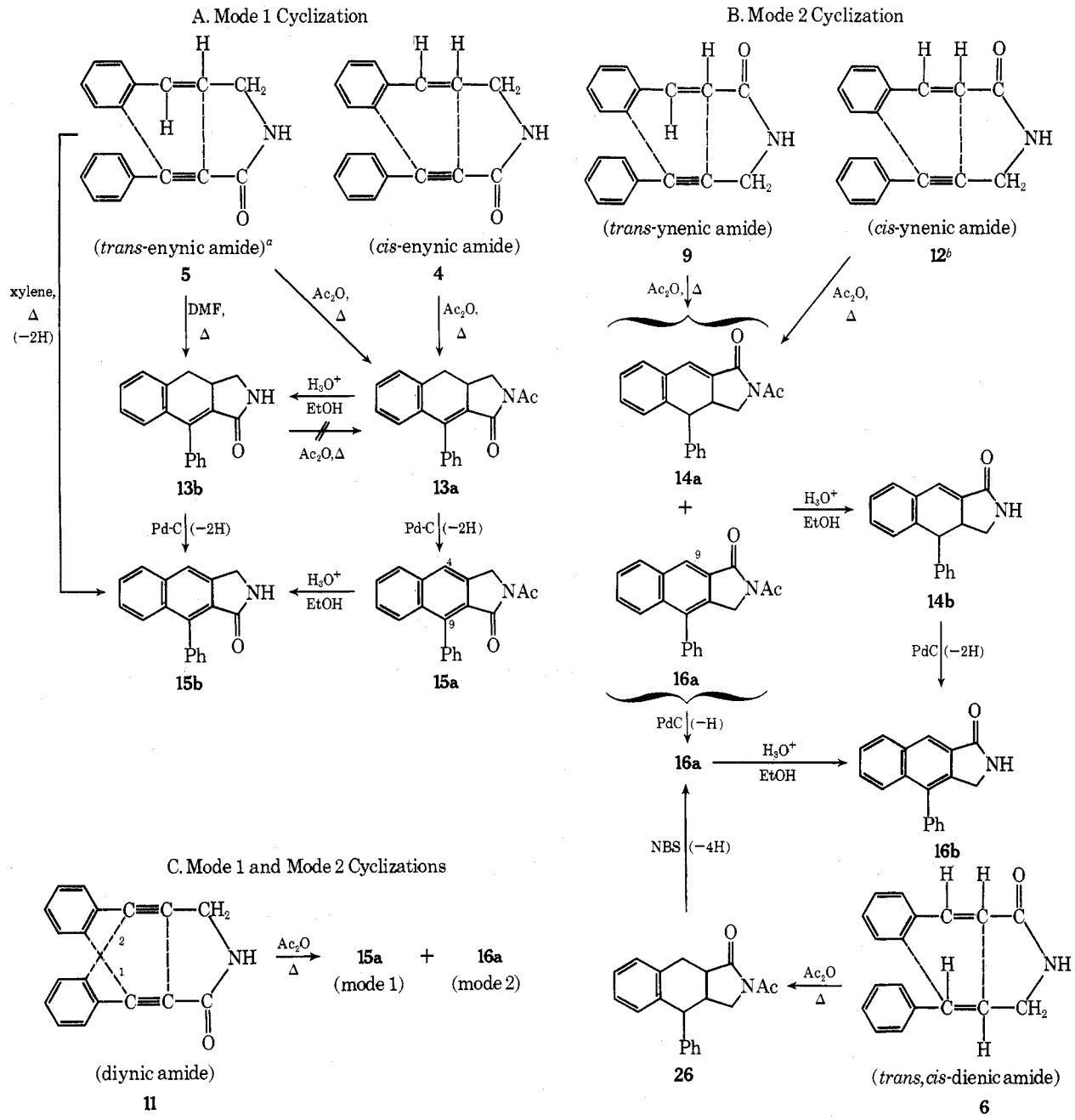


13c

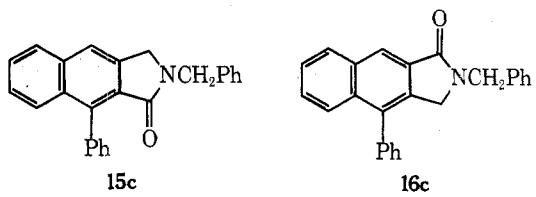


14c

Scheme I. Correlation of Structures in Cyclization Products from Amides

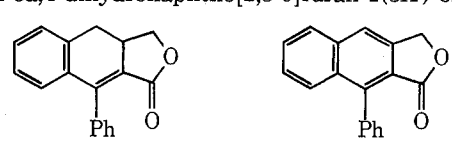


a The chemical natures of (C_2) and (C_3) (in the order given) are indicated beneath the formula. b A [2 + 2] cycloaddition product is also formed (cf. ref 8).



zation, and comparative data for analogous ester and *N*-benzyl amide cyclizations. A discussion of the relationships in Scheme I is presented in subsequent paragraphs.

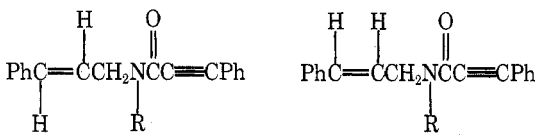
Cyclization of *N*-(*trans*-cinnamyl)phenylpropiolamide (**5**, $C_{18}H_{15}NO$) gave acetylated compound **13a** ($C_{20}H_{17}NO_2$), hydrolyzed to lactam **13b** ($C_{18}H_{15}NO$) on treatment with ethanolic hydrochloric acid. That cyclization had, indeed, occurred was apparent from the facts that the infrared spectrum of **13a** lacked bands for the C≡C and NH functions present in **5**, but exhibited carbonyl bands at 1690 and 1720 cm^{-1} (for an N-acetylated γ-lactam)[12d] in place of the original band at 1650 cm^{-1}. Deacetylated product **13b**, on the other hand, showed a single carbonyl band at 1700 cm^{-1}, as well as NH absorption at 3450 cm^{-1}. The ultraviolet spectra of **13a** and **13b**, moreover, were closely similar to the spectrum of 9-phenyl-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-one (**17**).[5]



Ultraviolet and infrared spectra, however, were insufficient to clearly distinguish **13a** and **13b** from the isomeric compounds **14a** and **14b** (respectively), products expected for cyclization by mode 2 rather than by mode 1 (as found). On the other hand, the ^1H NMR spectrum of the acetylated

product was consistent only with **13a** since it showed no evidence for the presence of a vinyl proton (expected for structure **14a**), though it did exhibit a singlet for the *N*-acetyl group at ca. δ 2.5. Final proof of structures **13a** and **13b** was obtained by dehydrogenation of these compounds to **15a** (88%) and **15b** (56%), rather than to **16a** and **16b**, by means of Pd/C in refluxing *p*-cymene. Product **15a** had a ^{1}H NMR spectrum which consisted of a ten-proton complex in the aromatic region of δ 7.1–8.0, a methylene singlet at δ 4.90, and an *N*-acetyl singlet at δ 2.57. In contrast, the ^{1}H NMR spectrum of **16a** should have included a singlet at ca. δ 8.3–8.5 for the aromatic proton at C-9[4] (vide infra). As expected, the ultraviolet spectra of **15a, 15b,** and 9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one[5] (**18**) were closely similar.

Cyclization of **5** is consistent with observations on the *N*-benzyl derivative **19b** and a large number of *trans*-enynic esters, all of which undergo cyclization in mode 1.[3-7,10,13-16]



19 **20**

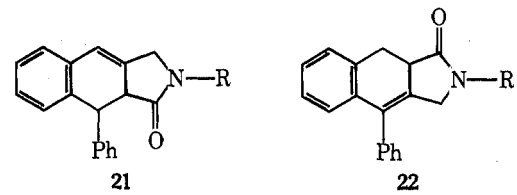
a, R = Ac; b, R = $PhCH_2$

For this reason, further studies on the conditions which foster cyclization of **5** were made. As expected for a thermal reaction, evaporative distillation of **5** at 240 °C gave **13b,** albeit in low yield (cf. observations made on a substituted *trans*-enynic ester).[15] Better results (55% yield of **13b,** 51% yield of **15b** formed by cyclization–dehydrogenation) were obtained in a solvent at 140–155 °C (refluxing dimethylformamide or xylene, respectively; cf. in situ ester cyclizations[13] in DMF), while cyclization did not occur in a solvent at ca. 80 °C (refluxing benzene or ethanol). When lactam **13b** was refluxed in acetic anhydride for 6 h no acetylation to form **13a** occurred. Instead, **13b** was recovered unchanged. When, however, open-chain amide **5** was treated with NaH in glyme at 0 °C and then with Ac_2O at 0–25 °C two products, **13a** (isolated yield 37%) and recovered **5,** were found. Neither TLC nor ^{1}H NMR analyses of the total reaction product mixture indicated the presence of any acetylated open-chain amide **19a** therein. It, therefore, appears that the reaction sequence in Ac_2O may be **5** → **19a** → **13a** (where the second step is much faster than the first one), but it is clearly not **5** → **13b** → **13a.** Previously, we noted that the *N*-benzyl derivative **19b** undergoes quantitative conversion into **13c** in refluxing Ac_2O and even cyclizes to a limited extent during recrystallization from ethyl acetate.[7] It is apparent, therefore, that substitution of an acetyl or a benzyl group on the nitrogen atom of **5** facilitates cyclization, perhaps by effecting a conformational change in the molecule which brings the dienic and dienophilic entities nearer to the configuration of the transition state.

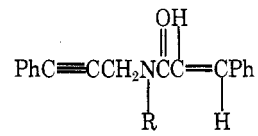
Cyclization of *N*-(*cis*-cinnamyl)phenylpropiolamide (**4,** an isomer of **5**) also gave **13a,** albeit in considerably lower yield. The possibility that formation of **13a** involves a preliminary rapid isomerization of **4** to **5** is unlikely, since interruption of the reaction after only 1 h of refluxing showed no spectral evidence for the presence of **5** in the total product mixture. From molecular models in seems probable that the reaction pathway is **4** → **20a** → **13a.** No other *cis*-enynic substrate has yet been used in our studies.

The diynic amide *N*-(phenylpropargyl)phenylpropiolamide (**6**) formed a solid reaction product which appeared to be a mixture of **15a** (cyclization mode 1) and **16a** (cyclization mode 2) in the ratio of 1.3:1, respectively, as based on ^{1}H NMR analysis (singlet for H-9 of **16a** at δ 8.48, two sets of methylene and acetyl singlets). Separation of these isomers was not accomplished, however. The combined yield (72%) of the isomers was surprising inasmuch as total product yields (one or two isolable isomers) varied from 14 to 39% in four other cases of diynic substrates.[4,5,7]

From Diels–Alder cyclization of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) one would expect to obtain either **21a** (mode 1) or **22a** (mode 2). Although a crystalline product (**24**)



21 **22**



23

a, R = Ac; b, R = H; c, R = $PhCH_2$

of narrow melting range (271–272 °C) and appropriate elemental composition was obtained, spectral evidence was inconsistent with either of the expected structures. Dehydrogenation of **24** with Pd/C led to a single product which was assigned structure **16a,** inasmuch as its ^{1}H NMR spectrum included a singlet for one proton at δ 8.48 plus other expected resonances for one component of the aforementioned mixture of **15a** and **16a** from cyclization of **6.** A 100-MHz ^{1}H NMR spectrum of **24** indicated that it was, indeed, a mixture of **14a** and **16a** in the molar ratio of ca. 4:1. This assignment was corroborated by ultraviolet and infrared spectra. The former spectrum of **24** was a composite of those of 3,4-dihydro-2-naphthoic acid[17] and **16a,** while the latter showed a medium-intensity band at 830 cm^{-1} (ascribed to C–H deformation in a trisubstituted alkene).[12b] Deacetylation of **24** produced crystalline **14b,** free of **16b** as based on ^{1}H NMR and ultraviolet spectra.

In previous investigations it was found that **23c,** the *N*-benzyl derivative of **9,** also cyclized in mode 2 to give a mixture (17% total) of **16c** and **22c.**[7] No **14c** was detected. The conversions **22a** → **14a** and **22c** → **14c** should be acid catalyzed.[18] Hence, formation of **14a** from **9** may be ascribed to the reaction sequence

$$9 + Ac_2O \rightarrow \mathbf{23a} + HOAc$$

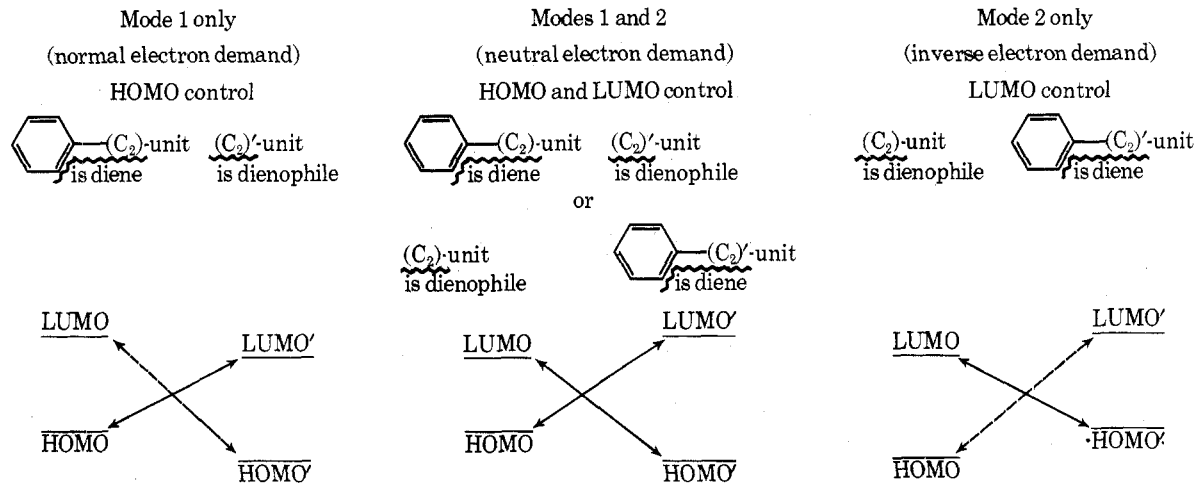
$$\mathbf{23a} \rightarrow \mathbf{22a} \xrightarrow{HOAc} \mathbf{14a}$$

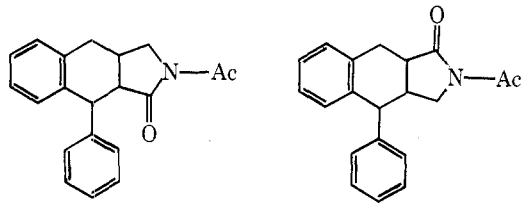
where the HOAc formed in the first step serves as a catalyst in the last step. In contrast, cyclization of **23c** to **22c** is not accompanied by the in situ formation of HOAc, and isomerization of **22c** to **14c** does not occur. It is noteworthy that phenylpropargyl *trans*-cinnamate, in contrast to **9** and **23c,** failed to undergo cyclization.[5]

Cyclization of *N*-(*trans*-cinnamyl)-*cis*-cinnamamide (**11**) produced a crystalline product with appropriate elemental and spectral properties for either structure **25** or **26** (stereochemistry not established). Oxidation of this substance with *N*-bromosuccinimide led to aromatic compound **16a** (rather than **15a**), consistent with the conversion **11** → **26** (cyclization in mode 2). In previous studies the ring-substituted compound *trans*-3,4-methylenedioxycinnamyl *cis*-3,4,5-trimethoxycinnamate was found to cyclize in mode 1 to give **27.**

Table II summarizes the modes of intramolecular [4 + 2] cycloadditions in corresponding amides (X = NH) and esters (X = O), as well as some *N*-benzyl amides (X = NCH_2Ph). Only five analogous cases[19] have thus far been investigated in each of the first two series (under comparable conditions

Scheme II. Proposed Frontier Orbital Relationships Involved in Modal Selectivity in Intramolecular [4 + 2] Cycloadditions of $Ph(C_2)CH_2OC(=O)(C_2)'Ph$ and $Ph(C_2)CH_2NHC(=O)(C_2)'Ph$





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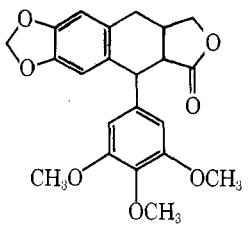

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of refluxing Ac_2O). For these cases, similar modes of cyclization were found in two systems (mode 1 for the *trans*-enynic compounds; a combination of modes 1 and 2 for the diynic compounds); no cyclization occurred for the *trans,trans*-dienic compounds; opposite modes of cyclization were found in one case (*trans,cis*-dienic compounds); cyclization vs. no cyclization occurred in one case (*trans*-ynenic compounds). It is clear that the ease and mode of intramolecular Diels–Alder reaction are markedly dependent on the nature of X, as well as on (C_2) and $(C_2)'$. One generalization which can be made on the basis of the results thus far obtained (including observations made on *N*-(phenylpropargyl)-*cis*-cinnamamide (**12**)[8] is that in either an enynic or an ynenic compound the C≡C unit assumes the role of the dienophile, in those cases where cyclization does occur. In the formalism of the Mulliken charge-transfer theory[20] electronic charge is transferred from the HOMO (highest occupied molecular orbital) of the diene (electron donor) to the LUMO (lowest unoccupied molecular orbital) of the dienophile (electron acceptor)[21] during the process of reaction. It has been noted repeatedly that the C≡C is less readily attacked by electrophiles than is the C=C.[22,23]

Considerations of regioselectivity are of pertinence in the intermolecular Diels–Alder reaction. They are not, however, of direct concern in the intramolecular Diels–Alder reaction on our substrates. Once the mode (1 or 2) of cyclization has been selected by one of our substrate molecules, conformational constraints (imposed through energetically allowed bond lengths and bond angles) would seem to permit [4 + 2] cycloaddition to occur in only one regioselective way.[24]

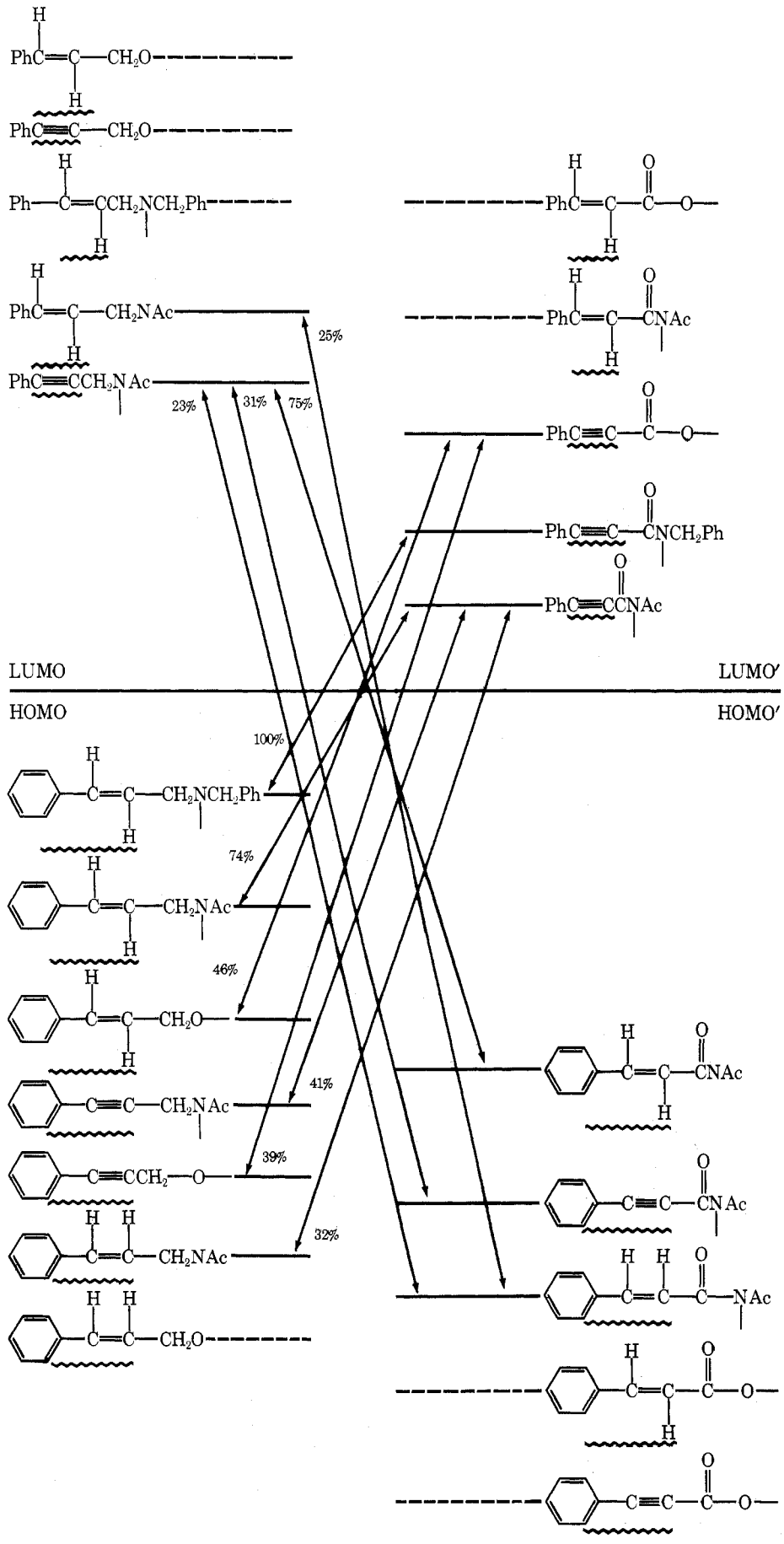
Contrariwise, modal selectivity can be interpreted qualitatively in terms of a modification of Sustmann's frontier orbital model,[25] as depicted in Scheme II. In this idealized scheme HOMO energy levels refer to the dienic unit in the $Ph(C_2)$ or $Ph(C_2)'$ moiety, while LUMO energy levels refer to the dienophilic unit (C_2) or $(C_2)'$. Frontier orbital energy levels are represented with different spacings for the (C_2) and $(C_2)'$ ends of the molecule and these orbital pairs may be shifted vertically with respect to one another. For the case of neutral electron demand cyclization in modes 1 and 2 are equally probable (as represented by two solid double-headed arrows which join orbitals that interact to significant extents). When electron demand of one end of the molecule surpasses that of the other end the orbital pairs shift so that one mode of cyclization prevails (solid arrow). The case of neutral electron demand is approximated by cyclization of diynic amide **6** and by some ring-substituted diynic esters which have been investigated.[4] Changing from an amide to an ester substrate (cf. Table II) or deleting substituents from the aromatic rings of the ester shift the ratio of mode 1/mode 2 cyclization away from a value of 1:1. As yet no systematic study of small variations in the diynic substrate molecules or of variations in the cyclizing medium on the modal ratio has been made. However, cyclization in mode 1 only or in mode 2 only can be considered to result from extreme modifications of the case of neutral electron demand.

Scheme III is an effort to depict (in a semiquantitative manner) the relative distributions of the frontier orbital energy levels for the (C_2) ends (left half of the scheme) and the $(C_2)'$ ends (right half of the scheme) of most of the substrate molecules listed in Table II. Omitted are some of the energy levels for *N*-benzyl substrates and for those (shown as broken lines) which are not pertinent to the cyclization processes. Cyclization in mode 1 is indicated by arrows which join levels in the upper right and lower left quadrants of the scheme, while cyclization in mode 2 is indicated by arrows which join levels in the upper left and lower right quadrants. In general, this scheme is constructed on the basis of the following anticipated relationships. (1) A (C_2) end is a better electron donor (upward displaced HOMO and LUMO energy levels) than is a $(C_2)'$ end (lower corresponding levels). (2) Of $(C_2)'$ units, the C≡C group is the strongest electron acceptor. (3) Of (C_2) units, the *trans*-CH=CH group is the strongest electron donor. (4) Yields of cyclization products generally increase with decreasing separation between the pertinent HOMO and LUMO energy levels, and vice versa.

Experimental Section[26]

Phenylpropargylamine Hydrochloride (2). *N*-(Phenylpropargyl)phthalimide was prepared from phenylpropargyl chloride[10] and K phthalimide in a manner similar to that previously described,[27] mp

Scheme III



152.5–153.5 °C (lit. 158–160 °C). A stirred mixture of 130 g of this imide, 17 g of hydrazine (95+%), and 1.3 l. of MeOH was refluxed for 2 h, allowed to cool, treated with 350 ml of concentrated hydrochloric acid, and refluxed 30 min longer. The mixture was cooled to 0 °C, filtered to remove precipitated phthalhydrazide (washed with cold MeOH), and evaporated to dryness. The residue was extracted with 500 ml of absolute EtOH at room temperature and the filtered extract was reevaporated. Crystallization of the residue from *i*-PrOH gave 70 g (84%) of platelets: mp 215–217 °C dec, raised to 216–217 °C dec on recrystallization from EtOH–Et_2O (1:1 v/v) (lit.[28] mp 216–217 °C); ν (KBr) 2250 (w, C≡C), 745 and 680 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.9–7.4 (m, 5 aromatic H), 4.81 (s, 3.8 H, NH_3^+ plus H_2O), and 4.25 (s, 2 H, methylene).

Anal. Calcd for $C_9H_{10}ClN$: C, 64.48; H, 6.01; Cl, 21.15; N, 8.36. Found: C, 64.25; H, 6.28; Cl, 21.52; N, 8.15.

***cis*-Cinnamylamine Hydrochloride (3).** A mixture of 0.25 g of 5% Pd/$BaSO_4$ (Baker), 0.2 ml of synthetic quinoline, and 40 ml of EtOH was agitated in hydrogen gas at 1 atm until the catalyst became black (ca. 1 h). A solution of 5 g of preceding amine salt **2** in 150 ml of EtOH was added and agitation was continued until 1 molar equiv of hydrogen was absorbed (ca. 3 h). The catalyst was removed by filtration and washed throughly with EtOH. Combined solutions were evaporated to leave a residue which was washed with ether and dried in vacuo (quantitative yield). Repeated crystallization from *i*-PrOH–Et_2O gave platelets: mp 169–170 °C (lit.[27] mp 177–178 °C); ν (KBr) 765 (s) and 690 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.6–7.2 (m, 5 aromatic H), 6.87 (d of t, J = 11.5 and 1.8 Hz, 1 H, CH=$CHCH_2$), 6.06 (d of t, 1 H, CH=$CHCH_2$), 5.12 (broad s, 3 H, NH_3^+), and 4.09 (d of d, J = 1.8 and 6.5 Hz, 2 H, methylene).

Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; Cl, 20.90; N, 8.26. Found: C, 63.46; H, 7.13; Cl, 20.95; N, 8.55.

Other Starting Materials. *trans*-Cinnamyl chloride[29] was converted successively into *N*-(*trans*-cinnamyl)phthalimide and *trans*-cinnamylamine hydrochloride[9] (**1**): ν (KBr) 960 (s, trans-disubstituted alkene), 735 and 685 cm^{-1} (s, 5 vicinal aromatic H); NMR (D_2O) δ 7.8–7.4 (m, 5 aromatic H), 6.96 (d, J = 16 Hz, 1 H, CH=$CHCH_2$), 6.49 (m, 1 H, CH=$CHCH_2$), 4.94 (s, 4.1 H, NH_3^+ plus H_2O), and 3.93 (d, J = 6.5 Hz, 2 H, CH=$CHCH_2$). *trans*-Cinnamoyl and phenylpropiolyl chlorides, obtained from the corresponding acids, were used immediately to form the amides.

cis-Cinnamic acid was obtained by hydrolysis of ethyl *cis*-cinnamate[11] with a refluxing solution of NaOH (15% excess) in 80% EtOH. The solution was concentrated in vacuo, treated with water, benzene, and 2 N H_2SO_4 (to pH 2), and shaken. The benzene layer was stored in the dark over Na_2SO_4 at 0–10 °C until needed (stable for 3 months or longer). Thereupon, the solution was evaporated in vacuo to give a viscous, red-brown liquid (89% yield, >95% cis by NMR spectrum). A solution of 4.4 g of this liquid in 50 ml of dry benzene was added dropwise to a stirred suspension of NaH (1.39 g, added as a 51.5% dispersion in mineral oil) in 50 ml of benzene in a nitrogen atmosphere at room temperature. After 2 more h of stirring the suspension was treated dropwise with a solution of 3.53 g of fresh, reagent grade $SOCl_2$ in benzene. This solution, containing *cis*-cinnamoyl chloride, was stirred 2 h longer and used directly in further reactions.

Syntheses of Unsaturated Amides. To a cold (0 °C), vigorously stirred suspension of 0.007–0.12 mol of amine hydrochloride (**1**, **2**, or **3**) in 100 ml of benzene were added (simultaneously and dropwise) solutions of (a) aqueous 2 N NaOH and (b) 0.01–0.13 mol of a crude, preceding acyl chloride in 100 ml of benzene. The molar ratio of amine hydrochloride to acyl chloride varied from 0.67 to 1.2. The total molar amount of NaOH used equaled that of the HCl formed. The mixture was stirred for 2 h at room temperature. The benzene layer was separated, washed successively with H_2O, dilute hydrochloric acid, 10% aqueous Na_2CO_3, and H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized repeatedly to constant melting range of 1 °C (Table I). Analytical and spectral data are presented in the following paragraphs.

Amide 4. ν 3450, 2230, 1650 cm^{-1}; λ_{max} 249 nm (log ϵ 4.52), 258 sh (4.45); NMR δ 7.7–7.1 (m, 10 aromatic H), 7.0–6.75 (broad m, 1 H, NH), 6.59 (d of t, J = 11.5 and 1.8 Hz, 1 H, CH=$CHCH_2$), 5.69 (d of t, 1 H, CH=$CHCH_2$), and 4.4–4.0 (2 overlapping d of d, J = 6.5, 5.5, and 1.8 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.73; H, 5.88; N, 5.68.

Amide 5. ν 3440, 3020, 2220, 1650, 965 cm^{-1}; λ_{max} 255 nm (log ϵ 4.55); NMR δ 7.6–7.0 (m, 10 aromatic H), 7.0–6.5 (broad, NH), 6.48 (d, J = 16 Hz, CH=$CHCH_2$), 6.12 (d of t, CH=$CHCH_2$) (3 H total for range 7.0–5.8), and 4.05 (t, J = 5.5 Hz, 2 H, CH=$CHCH_2$).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 83.04; H, 5.78; N, 5.68.

Amide 6. ν 3500, 2240, 1660 cm^{-1}; λ_{max} 242 nm (log ϵ 4.51), 252 (4.51); NMR δ 7.9–6.9 (m, 11 H, aromatic H plus NH) and 4.36 (d, J = 5.5 Hz, 2 H, CH_2NH).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.14, H, 5.23; N, 5.48.

***N*-(*cis*-Cinnamyl)-*trans*-cinnamamide (7).** A suspension of 250 mg of Lindlar catalyst[30] in 0.2 ml of synthetic quinoline and 40 ml of EtOAc was shaken with hydrogen gas at 1 atm for 1 h. A solution of 0.5 g of *N*-(phenylpropargyl)-*trans*-cinnamamide (**9**) in 100 ml of EtOAc was then added and agitation was continued until 1 molar equiv of hydrogen was absorbed (ca. 1 h). The catalyst was removed by filtration and washed with ethanol. Evaporation of the filtrate gave a solid which formed needles from aqueous EtOH, mp 136–137 °C (55%), raised to 137–138 °C on recrystallization, melting point undepressed on admixture with **7** from Schotten–Baumann synthesis; ν 3440, 1670, 975 cm^{-1}; λ_{max} 271 nm (log ϵ 4.49), 222 (4.33); NMR δ 7.62 (d, J = 16 Hz, CH=CHC=O) which overlaps 7.5–7.0 (m, 11 H total), 6.55 (d of t, J = 11.5 and 1.5 Hz, CH=$CHCH_2$) which overlaps 6.47 (d, J = 16 Hz, CH=CHC=O) and 6.7–6.4 (broad m, NH) (3 H total in region 6.7–6.3), 5.70 (d of t, J = 11.5 and 6.5 Hz, 1 H, CH=$CHCH_2$), and 4.5–4.1 (m, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51: N, 5.32. Found: C, 81.81; H, 6.55; N, 5.47.

Amide 8. ν 3440, 1670, 970 cm^{-1}; λ_{max} 268 nm (log ϵ 4.52), 222 sh (4.26), 216 (4.25); NMR δ 7.68 (d, J = 16 Hz, 1 H, CH=CHC=O) which partially overlaps 7.7–7.0 (m, 11 H, aromatic H plus NH), 6.68 (d, CH=CHC=O), 6.50 (d, J = 16 Hz, CH=$CHCH_2$) which partially overlaps 6.5–5.8 (m, CH=$CHCH_2$) (3 H total in region 6.9–5.8), and 4.10 (t, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 82.31; H, 6.40; N, 5.26.

Amide 9. ν 3450, 1660, 973 cm^{-1}; λ_{max} 242 nm (log ϵ 4.35), 251 (4.39), 279 sh (4.43), 273 (4.44); NMR δ 7.72 (d, J = 16 Hz, CH=CHC=O) which partially overlaps 7.7–7.0 (m, aromatic H plus NH), 6.61 (d, CH=CHC=O) (13 H total in region 8.0–6.4), and 4.45 (d, J = 5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 82.53; H, 5.80; N, 5.45.

Amide 10. ν 3440, 1660 cm^{-1}; λ_{max} 248 nm (log ϵ 4.35); NMR δ 7.6–7.0 (m, 10 aromatic H), 6.71 (d, J = 13 Hz, CH=CHC=O) which partially overlaps 6.49 (d of t, J = 12 and 1.5 Hz, CH=$CHCH_2$), 6.2–5.8 (broad m, NH) on which is superimposed 5.93 (d, CH=CHC=O) (2 H total in region 6.2–5.8), 5.52 (d of t, J = 12 and 6.5 Hz, CH=$CHCH_2$) (1 H in region 5.8–5.2), and 4.3–3.9 (m, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 82.43; H, 6.44; N, 5.39.

Amide 11. ν 3450, 1660, 965 cm^{-1}; λ_{max} 291 nm sh (log ϵ 3.77), 282 sh (3.96), 252 (4.45); NMR δ 7.6–7.0 (m, 10 aromatic H), 6.61 (d, J = 13 Hz, CH=CHC=O) and 5.89 (d, CH=CHC=O) which are superimposed on 6.8–5.6 (m, 5 H total, including CH=$CHCH_2$ and NH), and 3.89 (t, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{17}NO$: vide supra. Found: C, 81.78; H, 6.53; N, 5.36.

Amide 12. ν 3450, 1670 cm^{-1}; λ_{max} 223 nm (log ϵ 4.20), 250 (4.42), 240 (4.44); NMR δ 7.6–6.9 (m, 10 aromatic H), 6.72 (d, J = 12.5 Hz, 1 H, CH=CHC=O), 6.5–6.1 (broad m, 1 H, NH), 5.95 (d, 1 H, CH=CHC=O), and 4.20 (d, J = 5.5 Hz, 2 H, methylene).

Anal. Calcd for $C_{18}H_{15}NO$: vide supra. Found: C, 82.99; H, 5.92; N, 5.44.

2-Acetyl-9-phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (13a). A. Low-Dilution Method. A solution of 0.5 g of amide **5** in 4 ml of Ac_2O was refluxed for 6 h. Refrigeration of the cooled solution gave crystals which were washed with ice-cold Ac_2O and then with MeOH and dried: yield 0.264 g (46%); mp 182–184 °C; raised to 184–185 °C on recrystallization (prisms) from MeOH (Norit); ν 1720 and 1690 cm^{-1}; λ_{max} 308 nm (log ϵ 4.27), 240 (4.35); NMR δ 7.6–6.8 (m, 9 aromatic H), 4.5–4.0 (m, 1 H), 3.6–2.6 (m, 4 H), and 2.47 (s, 3 H, Ac); mass spectrum *m/e* 303 (100, M^+), 260 (33, $M^+ - Ac$), 232 (40), 231 (64), 218 (46), 203 (78, $C_{16}H_{11}^+$), 202 (74, $C_{16}H_{10}^+$), 43 (48, Ac^+).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.29; H, 5.56; N, 4.92.

B. High-Dilution Method. A solution of 0.5 g of amide **5** in 200 ml of Ac_2O was refluxed for 4 h and then evaporated to dryness in vacuo. The residue was crystallized from MeOH to give 0.45 g (74%) of **13a** as prisms, mp 179–180 °C.

C. Low-Temperature Method. A solution of 0.5 g of **5** in 25 ml of glyme was added dropwise to a stirred, cold (0 °C) mixture of 89 mg of NaH (used as a 51.5% dispersion in mineral oil) in 20 ml of glyme (nitrogen atmosphere). When hydrogen evolution ceased (15 min) a

mixture of 121 mg of Ac_2O in glyme (5 ml) was added dropwise. Stirring was continued at 0 °C for 15 min and then at room temperature for 2 h. The solvent was evaporated and the residue was extracted with $CHCl_3$. TLC (silica gel/$CHCl_3$) of the extract showed only two spots which corresponded to **5** and **13a**. Evaporation of the extract and recrystallization of the residue from EtOH gave 210 mg (37%) of needles of **13a**, mp 176.5–180 °C.

9-Phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (13b). A. From Deacetylation of 13a. A solution of 6 g of **13a** in 125 ml of concentrated hydrochloric acid and 315 ml of absolute EtOH was refluxed for 3 h and then evaporated. The residue was treated with water. The resultant solid was collected and crystallized from MeOH (crude yield 78%) to give needles: mp 238.5–239.5 °C; ν 3450, 1700 cm^{-1}; λ_{max} 295 nm (log ϵ 4.08), 235 (4.45); NMR (CF_3CO_2H) δ 7.7–6.8 (m, 10 H, aromatic H plus NH) and 4.4–2.7 (m, 5 H, aliphatic H); mass spectrum *m/e* 261 (100, M^+), 232 (46), 231 (54), 218 (32), 203 (70), 202 (59).

B. Directly from Amide 5. A solution of 0.5 g of amide **5** in 250 ml of DMF was refluxed for 6 h and then poured into water (300 ml). A $CHCl_3$ extract of the solution was washed with water, dried, and evaporated. Recrystallization of the residue from MeOH gave 315 mg (55%) of **13b**, mp 235–236 °C.

Evaporative distillation of 200 mg of **5** at 240 °C (0.01 Torr) over a period of 2 h gave 120 mg of crude **13b**, mp 234–235 °C after recrystallization from MeOH.

2-Acetyl-9-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (15a). A mixture of 1.2 g of **13a**, 0.6 g of 30% Pd/C, and 60 ml of *p*-cymene was refluxed and stirred for 30 h. The catalyst was separated and washed with more hot solvent. Concentration of the solutions gave 1.05 g (88%) of **15a**: mp 242.5–245.5 °C, raised to 250–251 °C on recrystallization (needles) from absolute EtOH; ν 3030, 1730, and 1690 cm^{-1}; λ_{max} 347 nm (log ϵ 3.63), 338 sh (3.58), 304 (4.00), 293 (4.00), 249 (4.84); NMR δ 8.0–7.1 (m, 10 aromatic H), 4.90 (slightly split s, $J \simeq$ 1 Hz, 2 H, CH_2N), and 2.57 (s, 3, Ac); mass spectrum *m/e* 301 (42, M^+), 259 (100, $M^+ - CH_2{=}C{=}O$), 223 metastable peak (301 → 259).

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.81; H, 4.94; N, 4.33.

9-Phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (15b). A. From 15a. Deacetylation of **15a** was effected as per **13a** to give platelets from absolute EtOH (71%): mp 258–259 °C; ν 3460, 1700 cm^{-1}; ν (KBr) 870 (lone aromatic H), 760, 750, 740, and 690 cm^{-1} (4 and 5 vicinal aromatic H); λ_{max} 335.5 nm (log ϵ 3.49), 322.5 (3.39), 300 (3.88), 289 (3.88), 278 sh (3.71), 241 (4.82); NMR δ 8.1–7.2 (m, 10 aromatic H), 7.0–6.75 (m, 1 H, NH), and 4.51 (broad s, 2, methylene); mass spectrum *m/e* 259 (100, M^+), 258 (64), 202 (40, $M^+ - CH_2NHC{=}O$).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.28; H, 5.40; N, 5.32.

B. From 13b. Dehydrogenation of **13b** was effected in the manner used with **13a**. Addition of petroleum ether (bp 30–60 °C) to the concentrated *p*-cymene solution gave 0.5 g (56%) of **15b**, mp 258–259 °C after recrystallization from EtOH.

C. From Amide 5. A solution of 498 mg of **5** in 300 ml of xylene was refluxed (N_2 atmosphere) for 5 h. The residue from evaporation of the solvent was crystallized from MeOH to give 255 mg (51%) of **15b**, mp 255–256 °C.

Cyclization of *N*-(*cis*-Cinnamyl)phenylpropiolamide (4). By the high-dilution method 1 g of amide **4** (in 700 ml of Ac_2O) gave a dark red gum. TLC of this crude product (silica gel/$CHCl_3$) showed only one fluorescent spot which corresponded to **13a**. Crystallization of the product from MeOH gave 368 mg (32%) of **13a** as needles, mp 183–184 °C.

Cyclization of *N*-(Phenylpropargyl)-*trans*-cinnamamide (9). The high-dilution method produced a 75% yield of platelets (**24**), mp 271–272 °C, from absolute EtOH. Product **24** was assigned the structure of a molecular compound (or eutectic mixture) containing about 20% of 2-acetyl-4-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (**16a**) and 80% of 2-acetyl-4-phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]-isoindol-1-one (**14a**): ν 1730, 1700 cm^{-1}; ν (KBr) 830 (trisubstituted alkene in **14a**), 760 and 700 cm^{-1} (4 and 5 vicinal aromatic H); λ_{max} 318 nm sh (log ϵ 4.07), 305 (4.16), 247 sh (4.15), 237 (4.27); NMR ($CDCl_3$, 100 MHz)[31] δ 7.8–6.6 (m, aromatic H plus H-9 in **14a**), 4.1–3.0 (m, aliphatic H), and 2.58 (s, Ac), plus singlets at 8.54 (H-9), 4.70 (methylene), and 2.71 (Ac) due to the presence of **16a**; mass spectrum *m/e* 303 (100, M^+ for **14a**), 261 (93, $M^+ - CH_2{=}C{=}O$), 259 (35), 204 (37), 203 (46), 202 (62), 178 (90), 43 (61, Ac^+).

Anal. Calcd for $4C_{20}H_{17}NO_2{\cdot}1C_{20}H_{15}NO_2$: C, 79.29; H, 5.52; N, 4.62. Found: C, 79.54; H, 5.74; N, 4.63.

2-Acetyl-4-phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (16a). Dehydrogenation of preceding mixture **24** by means of Pd/C in *p*-cymene was followed by washing the catalyst with $CHCl_3$. The concentrated filtrate was treated with cyclohexane and cooled to yield 82% of leaflets, mp 276–278 °C, converted to needles (mp 277–278 °C) on recrystallization from $CHCl_3$: ν 1730 and 1690 cm^{-1}; ν (KBr) 1730, 1690, 900 (lone aromatic H), 790 (4 vicinal aromatic H), 765 and 700 cm^{-1} (5 vicinal aromatic H); λ_{max} (dioxane) 347 nm (log ϵ 3.69) 332.5 (3.59), 304 (4.04), 293, (4.02), 282 sh (3.81), 250 (4.85); NMR δ 8.48 (s, 1 H at C-9), 8.3–7.2 (m, 9 aromatic H), 4.71 (s, 2, methylene), and 2.70 (s, 3 H, Ac); mass spectrum *m/e* 301 (37, M^+), 259 (100, $M^+ - CH_2{=}C{=}O$), 258 (41), 258–257 metastable peak (259 → 258).

Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.91; H, 5.09; N, 4.34.

4-Phenyl-2,3,3a,4-tetrahydro-1*H*-benz[*f*]isoindol-1-one (14b). Mixture **24** (594 mg) was deacetylated by refluxing in a solution of 7 ml of concentrated hydrochloric acid and 500 ml of absolute EtOH to give 431 mg (84%) of platelets: mp 284.5–287 °C dec from EtOH; ν 3440, 1700 cm^{-1}; ν (KBr) 1660, 830, 765, 750, 700 cm^{-1}; λ_{max} 293 nm (log ϵ 4.16), 233 (4.40), 227 (4.38); NMR (CF_3CO_2H) δ 8.3–6.7 (m, 11 H, aromatic H, NH, plus H-9) and 4.2–3.1 (m, 4 H); mass spectrum 261 (100, M^+), 259 (36), 204 (36), 203 (37), 202 (53), 178 (75). Neither the NMR nor the ultraviolet spectrum of this sample showed evidence for the presence of **16b** (vide infra).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73: H, 5.79; N, 5.36. Found: C, 82.77; H, 5.70; N, 5.19.

4-Phenyl-2,3-dihydro-1*H*-benz[*f*]isoindol-1-one (16b). Deacetylation of **16a** (vide supra) gave platelets (quantitative yield) from EtOH: mp 265–267 °C raised to 268.5–269.5 °C on recrystallization; ν 3460 and 1700 cm^{-1}; λ_{max} 334 nm (log ϵ 3.55), 318 (3.47), 298 (3.95), 287.5 (3.93), 238 (4.85); NMR (CF_3CO_2H) δ 8.60 (s, 1 H at C-9), 8.4–7.1 (m, 10 H, aromatic H plus NH), and 4.70 (broad s, 2 H, methylene); mass spectrum *m/e* 259 (100, M^+), 258 (53), 230 (33), 202 (32), 182 (57).

Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40. Found: C, 83.35; H, 5.15; N, 5.75.

Dehydrogenation of **14b** (vide supra) gave platelets (78%) of **16b**, mp 255–260 °C raised to 265–266 °C on recrystallization.

Cyclization of *N*-(Phenylpropargyl)phenylpropiolamide (6). Cyclization of **6** occurred at high dilution to yield a crude product which showed two overlapping spots by TLC (silica gel/$CHCl_3$). The NMR spectrum indicated the presence of a mixture of **15a** and **16a**. Integration of peaks at δ 8.48, 4.69, and 2.68 gave a ratio of 1:2:3 for signals from **16a**; and integration of peaks at 4.92 and 2.58 gave a ratio of 2:3 for those from **15a**. Integrations of the methylene signals gave a ratio of **15a**:**16a** 1.3:1. Recrystallization of the crude product from EtOH gave needles (72%): mp 240–248 °C; ν (KBr) 1730, 1690, 900, 765, 750, and 700 cm^{-1}. Efforts to effect separation of the mixture were unsuccessful.

2-Acetyl-4-phenyl-2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindol-1-one (26). Cyclization of amide **11** at high dilution (1 g in 1250 ml of Ac_2O) gave a red gum which crystallized from MeOH to form 290 mg (25%) of needles, mp 181–183 °C, converted to prisms (mp 185–186 °C) on recrystallization from the same solvent: ν 1735 and 1700 cm^{-1}; λ_{max} 306 nm (log ϵ 2.70), 252 sh (3.05); NMR δ 7.5–6.6 (m, 9 aromatic H), 4.1–2.7 (m, 7 aliphatic H), and 2.49 (s, 3 H, Ac).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.75; H, 6.25; N, 4.57.

Dehydrogenation of 26. A mixture of 73 mg of **26**, 85.2 mg of *N*-bromosuccinimide, 2 mg of benzoyl peroxide, and 25 ml of CCl_4 was refluxed (N_2 atmosphere) for 3 h, whereupon evolution of HBr ceased. The cooled solution was filtered (to remove succinimide) and evaporated. TLC (silica gel/$CHCl_3$:EtOAc 19:1) showed two fluorescent spots. The faster moving spot had an R_f value identical with that of **16a**. The other spot was not identified. Preparative TLC of 80 mg of reaction product gave 40 mg of needles of **16a**, mp 262–265 °C.

Miscellaneous Studies. Efforts to cyclize amide **8** at high dilution gave a red, viscous liquid which resisted efforts at crystallization. TLC showed only a smear and NMR spectrometry showed broad, unresolved multiplets.

Amine hydrochloride **3** (1 g) was treated with excess 5% aqueous Na_2CO_3 solution and the free *cis*-cinnamyl amine, which was collected by extraction into ether, was refluxed with 200 ml of Ac_2O for 6 h. Evaporation of the solvent and further processing gave a dark liquid, identified as *N*-acetyl-*N*-(*cis*-cinnamyl)acetamide by NMR analysis: (CCl_4) δ 7.4–7.0 (m, 5 aromatic H), 6.58 (d of t, J = 1.5 and 11.5 Hz, 1 H, CH=$CHCH_2$), 5.50 (overlapping d of t, J = 6 and 11.5 Hz, 1 H, $CH{=}CHCH_2$), 4.52 (d of d, J = 6 and 1.5 Hz, 2 H, methylene), and 2.13 (s, ~6 H, 2 Ac). This compound was not obtained analytically pure.

Registry No.—**1**, 4335-60-8; **2**, 30011-36-0; **3**, 4335-62-0; **13a**,

59015-40-6; **13b**, 59015-41-7; **14a**, 59015-42-8; **14b**, 59015-43-9; **15a**, 59015-44-0; **15b**, 59015-45-1; **16a**, 59015-46-2; **16b**, 59015-47-3; **24**, 59015-48-4; **26**, 59015-49-5; *N*-(phenylpropargyl)phthalimide, 4656-94-4; *trans*-cinnamoyl chloride, 17082-09-6; *cis*-cinnamoyl chloride, 59015-50-8; phenylpropiolyl chloride, 7299-58-3; *N*-acetyl-*N*-(*cis*-cinnamyl)acetamide, 59015-51-9; *trans*-cinnamyl chloride, 21087-29-6.

References and Notes

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Use of Substituted Benzyl Esters as Carboxyl-Protecting Groups in Solid-Phase Peptide Synthesis

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Benzyl esters have been widely used for the protection of side-chain carboxyl groups in peptide synthesis. This paper describes the evaluation of two substituted benzyl esters of glutamic acid in solid-phase peptide synthesis. The γ-*p*-chlorobenzyl ester of glutamic acid was found to be significantly more stable to trifluoroacetic acid cleavage than the benzyl ester, and yet it could be removed without difficulty by liquid HF at 0 °C. Hence it is recommended for side-chain protection of aspartic acid and glutamic acid residues in longer syntheses. Peptides with side-chain carboxyl groups protected by *p*-nitrobenzyl esters were prepared by solid-phase peptide synthesis followed by cleavage from the resin with HBr in acetic acid. Two protected peptides were synthesized by this approach, the tripeptide H-Gly-Glu(γ-OBzl-*p*-NO_2)-Ala-OH, and the amino-terminal hexapeptide from the acyl carrier protein of *E. coli*.

Protection of the side-chain carboxyl groups of aspartic and glutamic acids in peptide synthesis has been most commonly achieved by benzyl esters.[1] This protection is very suitable, in that it is fairly stable to the conditions of peptide synthesis, and it can be removed at the end of the synthesis by strongly acidic or reducing conditions.[2]

There are important reasons, however, for seeking alternative carboxyl-protecting groups, for it has been shown[3–5] that benzyl esters are not completely stable to the conditions commonly used to remove the *t*-Boc[6,7] group during peptide synthesis. This lability gives rise to a cumulative loss of side-chain protection, and increases the possibility of branching of the peptide chain, particularly during a long synthesis.

An important potential use of more stable carboxyl-protecting groups is in the synthesis of protected peptides, which can be used in fragment syntheses and semisynthesis of proteins.[8–12] In an attempt to develop a simple method for the preparation of protected peptides, it was decided to examine the synthesis of a fully protected peptide using standard solid-phase techniques. If the side chains and amino terminus of a peptide were blocked by groups stable to acidolysis, the synthesis could be performed on a chloromethylated resin, with the usual *t*-Boc group for α-amino protection, and using HBr in acetic acid for the cleavage of the peptide from the resin.

This paper describes the evaluation of two acid-stable carboxyl-protecting groups: the *p*-chlorobenzyl ester as a group of moderately increased stability for use in longer syntheses, and the *p*-nitrobenzyl ester as a much more stable group for the synthesis of protected peptides with HBr