Intramolecular Diels-Alder Reactions. IX. Syntheses of *N*-Benzylcyclolignan Lactams (1)

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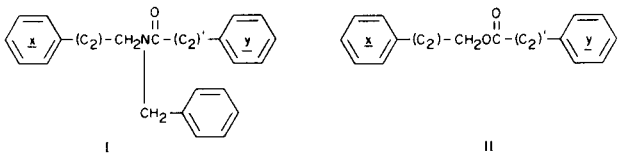
Four bis-unsaturated *N*-benzyl amides of the type $Ph(C_2)CH_2NCO(C_2)'Ph$, where (C_2) and $(C_2)'$ are variously *trans*-CH=CH and C≡C groups, were synthesized and refluxed in acetic anhydride. Three of them cyclized to form *N*-benzylcyclolignan lactams by intramolecular Diels-Alder processes. In one case [(C_2) = C≡C, $(C_2)'$ = *trans*-CH=CH] the (C_2) unit functioned as the dienophilic moiety.

In continuation of our studies on the intramolecular Diels-Alder reaction we have investigated the syntheses and cyclizations of four bis-unsaturated *N*-benzyl amides of the general formula I, wherein the (C_2) and $(C_2)'$ units are variously C≡C and *trans*-CH=CH moieties. Amides I are analogs of the bis-unsaturated esters II, which have previously been studied in our laboratory (3,4). Compounds IIa and IIc [as well as many of their ring-substituted derivatives (3-8)] underwent facile Diels-Alder cyclization

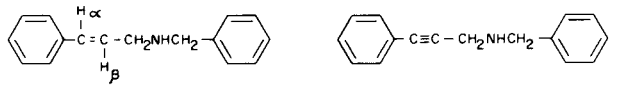


I II

a: (C_2) = $(C_2)'$ = C≡C b: (C_2) = C≡C; $(C_2)'$ = *trans*-CH=CH
c: (C_2) = *trans*-CH=CH; $(C_2)'$ = C≡C d: (C_2) = $(C_2)'$ = *trans*-CH=CH

in refluxing acetic anhydride or dimethylformamide. On the other hand, IIb and IId (plus many derivatives of the latter) failed to cyclize under any conditions tried.

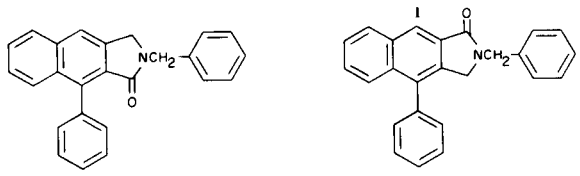
Used in the syntheses of amides I were benzyl*trans*-cinnamylamine (III) and benzylphenylpropargylamine (IV), obtained from benzylamine by alkylation with *trans*-cinnamyl and phenylpropargyl chlorides, respectively.



III IV

Schotten-Baumann reaction of III and IV with *trans*-cinnamoyl and phenylpropiolyl chlorides yielded the amides (Ia-Id) as gums, employed directly in cyclization studies.

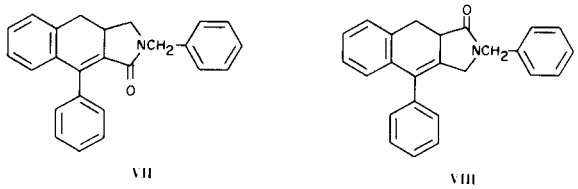
Refluxing diynic amide Ia with acetic anhydride gave lactam V (14% from IV). Assignment of structure V (rather than the alternative possibility VI) to the product



V VI

was based on the pmr spectrum, which showed no signal at $\delta > 8.0$ ppm. Had VI been obtained (*vide infra*) a singlet for H-1 should have been apparent at *ca.* 8.4 ppm (6).

Amide Ic cyclized very readily. In fact, an effort to recrystallize Ic from ethyl acetate gave instead a 29% yield of lactam VII, while refluxing Ic in acetic anhydride



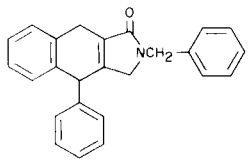
VII VIII

produced a quantitative yield of VII. As expected, treatment of VII with palladium-charcoal in refluxing *p*-cymene gave dehydrogenation to V.

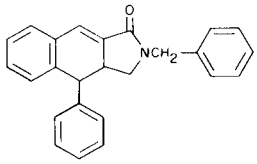
Two modes of intramolecular Diels-Alder cyclization are possible for bis-unsaturated amides I (or esters II). Mode 1 (which might be called "normal" cyclization) involves the action of the $(C_2)'$ unit as the dienophile and ring *x* plus the (C_2) unit as the diene. Mode 2 (or "abnormal" cyclization) involves the action of the (C_2) unit as the

dienophile and ring *y* plus the $(C_2)'$ unit as the diene. While amides Ia and Ic underwent cyclization according to mode 1, this was not the case for Ib, which cyclized to a crystalline product, *A*, m.p. 187-188°. Dehydrogenation of *A* produced compound VI (24% overall yield from IV), derived by cyclization according to mode 2 and identified by the presence of singlets for H-1 at δ 8.43 (6), for the benzyl methylene group at 4.79, and for the lactam methylene group at 4.17 ppm (as well as a multiplet for other aromatic protons).

It was readily apparent that *A* contained more than one component, since the pmr spectrum was rather complex. The presence of VI therein was evident from clear singlets at 8.43, 4.79, and 4.17 ppm. The mass spectrum of *A* indicated that there were present two components, VI (parent ion at m/e 349, relative abundance 65%) and dihydro-VI (presumably VIII, IX, or X; parent ion at m/e 351, relative abundance 100%). Total integration of aromatic and aliphatic protons in the pmr spectrum was consistent with the composition of dihydro-VI:VI = 2:1 for *A*. Final structural assignment to *A* was based on its



IX



X

ultraviolet absorption spectrum. For comparison purposes, the reported spectra of 1-phenyl-3,4-dihydronaphthalene (9), 2-methylcyclohexene-1-carboxylic acid (10), and 3,4-dihydro-2-naphthoic acid (11) (as models for VIII, IX, and X, respectively) were used, along with the measured spectrum of VI. If one limits consideration to the presence of just two components, then the relationship *A* ≡ 2VIII·1VI is consistent with all of these data. It is presumed that the primary cyclization product from Ib is VIII, which partially undergoes spontaneous dehydrogenation (during the reflux period) to give VI and, thereby, to form the crystalline binary product *A*. Efforts to separate *A* into its constituents were unsuccessful.

The *trans,trans* amide Id, like its ester counterpart IId, failed to cyclize in refluxing acetic anhydride.

EXPERIMENTAL (12)

Benzyl*trans*-cinnamylamine (III).

To 38.1 g. (0.36 mole) of cold (0°), stirred anhydrous benzylamine (dried over potassium hydroxide pellets) was added dropwise 10.9 g. (0.072 mole) of *trans*-cinnamyl chloride. The mixture was diluted with 75 ml. of benzene, refluxed for one hour, cooled, and filtered. The filtrate, plus benzene washings of the crystalline amine salts, was washed with water, dried (sodium sulfate), and distilled. The nearly colorless liquid (12.2 g., 76%) of b.p. 145-147° (0.4 mm.) was collected as the product III; ir (carbon tetrachloride) 3340 (NH), 965 cm^{-1} (*trans*-CH=CH); pmr (carbon tetrachloride) δ 7.5-6.9 (m, 10, aromatic protons), 6.46 (d, J = 16 Hz, 1, H_α), 6.06 (pseudo d of d, J = 5 Hz, J = 16 Hz, 1, H_β), 3.67 (s, 2, benzyl methylene), 3.22 (d, J = 5 Hz, cinnamyl methylene), 1.14 ppm (s, 1, NH).

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.1; H, 7.7; N, 6.3. Found: C, 85.9; H, 7.6; N, 6.1.

A benzamide derivative formed needles from absolute ethanol, m.p. 78.5-79.5°.

Anal. Calcd. for $C_{23}H_{21}NO$: C, 84.4; H, 6.5; N, 4.3. Found: C, 84.3; H, 6.7; N, 4.2.

Benzylphenylpropargylamine (IV).

To a stirred solution (at room temperature) of 17.8 g. (0.17 mole) of anhydrous benzylamine in 25 ml. of benzene was added dropwise 5 g. (0.033 mole) of phenylpropargyl chloride (13). The mixture was stirred and refluxed for 2 hours and then processed as for III, yield 5 g. (68%) of nearly colorless IV, b.p. 141-143° (0.2 mm.); positive Hinsberg test for a secondary amine (14). Further distillations gave an analytically pure sample; ir (carbon tetrachloride) 3340 (NH), 1600, 1490, 1450 cm^{-1} (aromatic rings); pmr (carbon tetrachloride) δ 7.5-6.9 (m, 10, aromatic protons), 3.78 (s, 2, benzyl methylene), 3.46 (s, 2, phenylpropargyl methylene), 1.35 ppm (s, 1, NH).

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.8; H, 6.8; N, 6.3. Found: C, 86.8; H, 7.1; N, 6.2.

N-Benzyl-1-phenyl-3-aminomethyl-3,4-dihydro-2-naphthoic Acid Lactam (VII).

To a cold (0°), stirred solution of 0.03 mole of phenylpropiolyl chloride (3) in 13 ml. of benzene were added dropwise and simultaneously 5.8 g. (0.026 mole) of amine III and 13 ml. of 2*N* sodium hydroxide (0.026 mole). The mixture was stirred for 1.5 hours longer. The benzene layer (plus benzene extracts of the aqueous layer) was washed successively with water, dilute hydrochloric acid, 5% aqueous sodium carbonate and water. Evaporation of the dried solution gave a brown, viscous liquid which consisted of a mixture of Ic [ir (carbon tetrachloride) 2240 cm^{-1} (C≡C), 1625 (tertiary amide) (15)] and VII.

A portion of the crude mixture was crystallized (by heating) from ethyl acetate to give yellow needles of VII (29% from III), m.p. 132-135°, converted to white prisms on recrystallization, m.p. 139.5-140.5°; ir (chloroform) 1680 cm^{-1} (γ-lactam); uv max 302 nm (log ε = 4.20), 237 (4.29), 230 (4.26, shoulder); pmr δ 7.37 and 7.23 (2 s) superimposed on 7.5-6.8 (m, 14 total, aromatic protons), 4.46 (d of d, J = 15 Hz, 2, benzyl methylene), 3.7-2.4 ppm (m, 5, other aliphatic protons).

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.4; H, 6.0; N, 4.0. Found: C, 85.5; H, 6.1; N, 4.3.

A solution of another portion (1 g.) of the preceding crude mixture in 8 ml. of acetic anhydride was refluxed for 5 hours. The residue from evaporation (*in vacuo*) of the solvent was recrystallized from ethyl acetate to give 1 g. (quant. yield) of VII, m.p. 135-136°, raised to 139.5-140.5° on recrystallization, undepressed on admixture with product from the preceding paragraphs.

N-Benzyl-1-phenyl-3-aminomethyl-2-naphthoic Acid Lactam (V).

A. From Dehydrogenation of VII.

A mixture of 1.3 g. of dihydro compound VII, 0.6 g. of 30% palladium-charcoal, and 75 ml. of *p*-cymene was refluxed for 50 hours. Evaporation of the filtered solution gave a solid which was

crystallized from absolute ethanol to form 0.6 g. (46%) of V, obtained as needles, m.p. 171.5-172.5°; ir (potassium bromide pellet) 875 (lone aromatic hydrogen atom), 760 and 700 cm^{-1} (four and five vicinal aromatic hydrogen atoms); ir (chloroform) 1690 cm^{-1} (γ-lactam); uv max 241 nm (log ε = 4.94) shoulder, 245 (4.95), 291 (4.21), 302 (4.22), 323 (3.63), 337 (3.70); pmr δ 7.45 and 7.24 (2 s) superimposed on 7.9-6.8 (m, 15 total, aromatic protons), 4.71 (s, 2, benzyl methylene), 4.29 ppm (s, 2, lactam methylene).

Anal. Calcd. for $C_{25}H_{19}NO$: C, 85.9; H, 5.5; N, 4.0. Found: C, 86.0; H, 5.5; N, 3.8.

B. From Cyclization of Amide Ia.

In the manner used to prepare Ic there was obtained (from phenylpropiolyl chloride and 5 g. of amine IV) a red gum which consisted of a mixture of Ia [ir (carbon tetrachloride) 2230, 1650 cm^{-1}; characteristic pmr signals at δ 4.90 (s, benzyl methylene) and 4.44 ppm (s, phenylpropargyl methylene)] and V. Refluxing this mixture in acetic anhydride (1 l.) for 6 hours, evaporation of the solvent, and recrystallization of the residue from ethanol gave 1.14 g. (14%) of V, m.p. 163-166°, raised to 171.5-172.5° on recrystallization, undepressed on admixture with product from part A.

Cyclization of *N*-Benzyl-*N*-phenylpropargyl-*trans*-cinnamamide (Ib).

Schotten-Baumann reaction between *trans*-cinnamoyl chloride and amine IV (5.5 g.) gave 8.4 g. (96%) of crude Ib [obtained as a red-yellow viscous liquid; ir (carbon tetrachloride) 1660 (tertiary amide), 970 cm^{-1} (*trans*-CH=CH)]. Cyclization of 3.6 g. of this amide in acetic anhydride and crystallization of the product from ethyl acetate gave 0.596 g. (17%) of product, m.p. 164-166°. Tlc on alumina with chloroform-benzene (1:1) as eluent revealed a single fluorescent spot [probably due to the presence of lactam VI]. Recrystallization from ethanol gave prisms of *A*, m.p. 177-178°, raised to 187-188° on drying at 100° *in vacuo*, assigned the structure of a mixture (possibly a molecular complex) containing 2 VIII:1 VI; ir (chloroform) 1690 cm^{-1} (γ-lactam); uv max 229 nm (log ε = 4.45), 238 (4.43) shoulder, 268-276 (3.97), 320 (2.99), 336 (3.02); pmr δ 8.43 (s, *ca.* 0.5, H-1 in VI), 7.24 (sharp s) superimposed on 7.7-6.8 (m, aromatic protons), 4.9-2.7 ppm (complex m, aliphatic protons), total integration for ratio of aromatic protons/aliphatic protons; found: 2.3; calcd. for 2:1-mixture: 2.39.

Anal. Calcd. for 2 $(C_{25}H_{21}NO)$·1$(C_{25}H_{19}NO)$: C, 85.6; H, 5.9; N, 4.0. Found: C, 85.8; H, 5.7; N, 4.0.

N-Benzyl-4-phenyl-3-aminomethyl-2-naphthoic Acid Lactam (VI).

Crude product from the cyclization of Ib (3.2 g.) was dehydrogenated with palladium-charcoal in refluxing *p*-cymene and in a nitrogen atmosphere. Evaporation of the filtrate plus chloroform washings of the catalyst gave a viscous liquid which crystallized from ethanol to produce 0.8 g. (25%) of VI, m.p. 161-163°, converted to pale yellow-green needles (m.p. 162.5-163.5°) on further crystallization; ir (chloroform) 1680 cm^{-1} (γ-lactam); uv max 243 nm (log ε = 4.84), 289 (4.05), 300 (4.05), 320 (3.49), 336 (3.53); pmr δ 8.43 (s, 1, H-1), 7.26 (sharp s) superimposed on 8.2-7.1 (m, 14 total, aromatic protons), 4.79 (s, 2, benzyl methylene), 4.17 ppm (s, 2, lactam methylene).

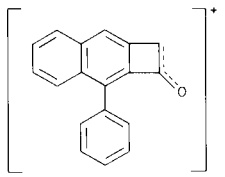
Anal. Calcd. for $C_{25}H_{19}NO$: C, 85.9; H, 5.5; N, 4.0. Found: C, 85.6; H, 5.6; N, 4.2.

Studies on Amide Id.

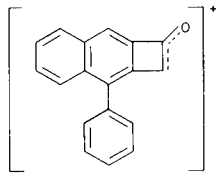
Reaction of *trans*-cinnamoyl chloride with amine III in the preceding manner gave a yellow glass, crude *trans,trans* amide Id; ir (chloroform) 1650 (tertiary amide), 985 and 970 cm^{-1} (two *trans*-CH=CH groups); pmr δ 7.87 (d, *J* = 16 Hz), 7.6-6.9 (m, aromatic protons), 6.8-6.1 (m, vinyl protons), 4.73 (broad s, 2, benzyl methylene), 4.4-4.0 ppm (m, 2, cinnamyl methylene); one spot on tlc with silica gel-chloroform; apparently unchanged on refluxing in acetic anhydride.

Mass Spectra of Lactams.

Mass spectra were determined by means of a CEC model 21-110 instrument at 70 eV. Only peaks of relative abundance ≥15% of the most abundant peak are reported here. Aromatic lactams V and VI showed similar fragmentation patterns: for V, m/e (relative abundance), 350 (29), 349 (100, M^+), 258 (29 $[M\text{-}C_6H_5\text{-}CH_2]^+$), 245 (40, XI^+), 215 (22), 202 (18, $XIII^+$), 91 (48, $C_7H_7^+$); for VI, 350 (28), 349 (100), 258 (44), 245 (34, XII^+), 216 (23), 215 (40), 202 (25), 91 (74).

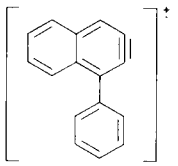


XI+

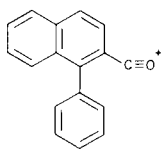


XIII+

The spectrum of dihydro compound VII was also relatively simple with peaks at 352 (27), 351 (100, M^+), 232 (16), 231 (34, XIV^+), 204 (15), 203 (35), 202 (25), 91 (39). However, the spectrum of product *A* was more complex: 352 (29), 351 (100, $VIII^+$), 350 (29), 349 (65, VI^+), 258 (24), 245 (18), 219 (19), 218 (77 $[M\text{-}C_6H_5CH_2N{=}C{=}O]^+$), 217 (85), 216 (23), 215 (46), 204 (20), 203 (33), 202 (42), 91 (87), 65 (15).



VIII+



XIV+

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(1) This investigation was supported by research grant No. GM 12730 from the National Institutes of General Medical Sciences, U.S. Public Health Service. For Paper VIII see ref. 8. Our use of the term "cyclolignan lactam" is consistent with that of "cyclolignan lactone," as defined in reference 2 or Paper VIII. Cyclolignan lactams have not been found in nature.

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