Studies in Sesquiterpene Synthesis.[1] The Marasmic Acid Skeleton

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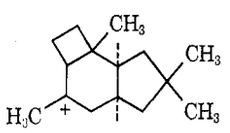
A route to the marasmic acid skeleton which uses as a key reaction Diels–Alder additions to β-(4,4-dimethyl-1-cyclopentenyl)acrylic acid and its derivatives is described.

A growing number[4] of fungal metabolites have been isolated from the Basidiomycetes (true mushrooms). These compounds may be thought to arise by a new mode of cyclization of a humulene-type precursor to give ion **1**.



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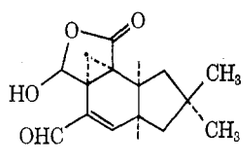

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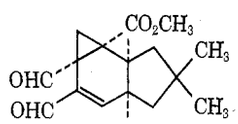

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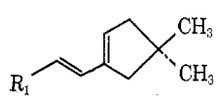
In a general survey[5] of the Basidiomycetes for antibacterial activity, a crystalline compound was found which possessed marked activity against *Staphylococcus aureus*. This substance, isolated from *Marasmius conigenus*, was partially characterized at that time and called marasmic acid. However, because its antibacterial activity decreased markedly in the presence of blood and because it was highly toxic, marasmic acid was not further investigated.

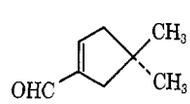
In 1965 de Mayo and others[6] reported the reisolation and characterization of marasmic acid. Its true structure (**2**) and stereochemistry were determined. A final point of the stereochemistry of marasmic acid was reported recently by Sim[7] in an X-ray analysis of a marasmic acid derivative.

Although synthetic efforts toward some Basidiomycete sesquiterpenes, notably the illudins,[8] have been successful, and a synthesis of illudol[9] has appeared, only a synthesis of methyl isomarasmate[10] (**3**) has been reported. This isomer differs from the marasmic acid series in the crucial cis relationship of the cyclopropane ring to the hydrogen at the ring fusion. We wish to report efforts in our laboratory directed toward a stereoselective synthesis of the crucial ring system.

Our route to the marasmic acid system involves as a key reaction the Diels–Alder addition of a suitable dienophile to dienes **4a–e**. The required hydrindan ring system (**6**) is formed, the three functionalized carbons are incorporated, and a reactive group for the introduction of the three-membered ring is generated in one operation. For simplicity at the early stages of the investigation the system selected was $R_1 = R_2 = R_3 = COOCH_3$. Thus the dienophile is dimethyl acetylenedicarboxylate and the diene required is *trans*-β-(4,4-dimethyl-1-cyclopentenyl)acrylic ester (**4a**). Since diene **4a** could be transformed into other diene derivatives by hydrolysis, reduction, etc., compound **4a** was the initial target of synthesis.



4a, $R_1 = COOCH_3$
b, $R_1 = COOH$
c, $R_1 = CH_2OH$
d, $R_1 = CH_2OCOPh$
e, $R_1 = CH_2O$-3,5-dinitrobenzoate



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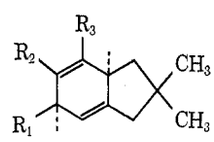

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The required diene was made by Wittig reaction of **5** with $Ph_3PCHCOOCH_3$[11] to form **4a** in 87% distilled yield.[12] The several routes to **5** are outlined in Scheme I. Compound **4a** was hydrolyzed to the acid **4b** and reduced with diisobutylaluminum hydride[13] to alcohol **4c**. When compound **4b** was treated with diazomethane, **4a** was regenerated. When alcohol **4c** was treated with PhCOCl or 3,5-dinitrobenzoyl chloride in pyridine, derivatives **4d** and **4e**, respectively, were obtained. Thus, with a variety of dienes available, the task of constructing the bicyclic ring system was undertaken.

When compound **4a** was refluxed in benzene solution containing excess dimethyl acetylenedicarboxylate for 3 days under nitrogen, or heated neat with the acetylene overnight at 100°, a Diels–Alder reaction occurred to give adduct **7**. In addition, variable amounts of compounds **8** and **9** were formed. (The stereochemistry of **7** must be as indicated because of the mechanism of the Diels–Alder reaction.) A slight excess of diene **4a**

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(3) Deceased, December 22, 1971.

(4) (a) M. Anchel, *et al.*, *Phytochemistry*, **9**, 2339 (1970); (b) M. Anchel and T. C. McMorris, *J. Amer. Chem. Soc.*, **87**, 1594 (1965); (c) S. Matsumoto, *et al.*, *Tetrahedron Lett.*, 3913 (1969); (d) T. C. McMorris, *et al.*, *J. Amer. Chem. Soc.*, **89**, 4562 (1967); (e) T. C. McMorris, *et al.*, *J. Org. Chem.*, **34**, 240 (1969); (f) S. Takahashi, *et al.*, *Tetrahedron Lett.*, 1637 (1970); (g) H. Matsumoto, *et al.*, *ibid.*, 3125 (1971); (h) G. Magnusson, *et al.*, *ibid.*, 1105 (1972); (j) M. S. R. Nair and M. Anchel, *ibid.*, 2753 (1972).

(5) W. J. Robbins, *et al.*, *Proc. Nat. Acad. Sci. U. S.*, **35**, 343 (1949).

(6) P. de Mayo, *et al.*, *J. Amer. Chem. Soc.*, **88**, 2838 (1966), and references cited therein.

(7) G. A. Sim and P. D. Cradwick, *Chem. Commun.*, 431 (1971).

(8) T. Matsumoto, *et al.*, *Tetrahedron Lett.*, 2049 (1971).

(9) T. Matsumoto, *et al.*, *ibid.*, 3521 (1971).

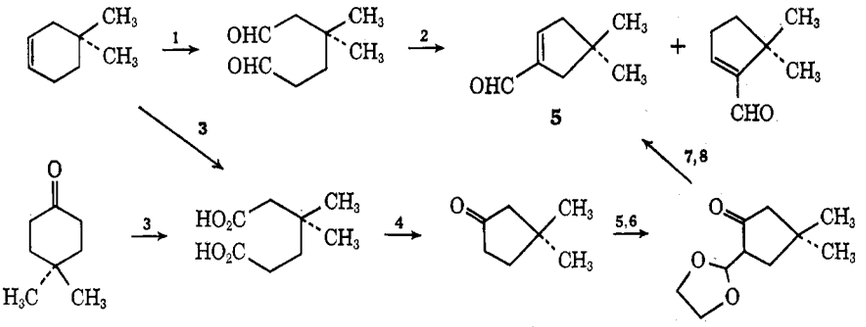
(10) P. de Mayo, *et al.*, *ibid.*, 349 (1970).

(11) P. Zeller, *et al.*, *Helv. Chim. Acta*, **40**, 1247 (1957).

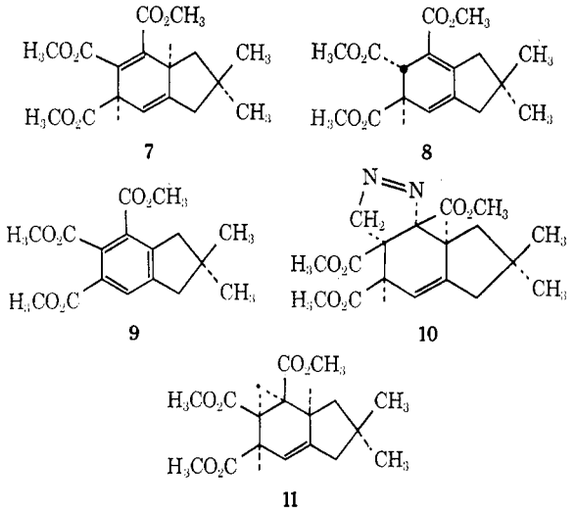
(12) All compounds possessed spectral data consistent with the assigned structures (see Experimental Section).

(13) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **88**, 1458 (1966).

SCHEME I[a]



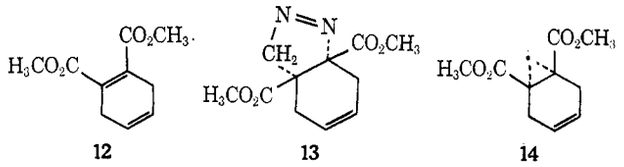
[a] 1, IO_4^{2-}, OsO_4; 2, piperidine–acetic acid; 3, $KMNO_4$; 4, potassium fluoride; 5, HCO_2Et, NaH; 6, ethylene glycol, H^+; 7, $NaBH_4$; 8, H_3O^+. *Cf.* ref 18.



and dimethyl acetylenedicarboxylate was sealed in a glass tube under vacuum, and heated at 60° for 2 weeks. Practically pure (>95%) **7** was obtained in this way and could be used in the next step without further purification.

With compound **7** in hand, the construction of the three-membered ring by diazomethane addition[14] and subsequent photolysis was envisioned. Since marasmic acid requires the cyclopropane to be cis to the adjacent proton and thus on the bottom side of the molecule as it is drawn, and since the decomposition of the Δ^1-pyrazoline is stereospecific, the addition of diazomethane to **7** must occur on the bottom side. The conformation of **7** is such that exo addition is expected and probably the least hindered approach of the 1,3 dipole would result in compound **10**. Decomposition of **10** would give the marasmic acid skeleton **11**.

At this point, we decided to turn to the model system **12**. When compound **12** was allowed to contact ethereal diazomethane at room temperature for 2 weeks, addition occurred exclusively to the conjugated double bond, giving adduct **13**. Thick layer chromatography (silica gel) of **13** gave pure material, mp 74–75°. The nmr showed a diagnostic methylene AB quartet centered at δ 4.75 (J_{AB} = 18 Hz) and the uv spectrum showed a fairly sharp absorption, λ_{max} 318 nm (ϵ 184), characteristic[15] of the azo group. When **13** was injected into the vpc (injection port temperature 240°), or was irradiated in dilute ether solution through quartz, a single compound **14**[16] was formed in nearly quantitative yield.



Encouraged by the success of the model system, we allowed compound **7** to contact ethereal diazomethane solution at room temperature. After 9 days the ether and excess diazomethane were evaporated to yield **10** in 70% yield.[17] No evidence of more than one pyrazoline could be found. Photolysis of **10** in dilute ether solution in a quartz vessel gave excellent yield of marasmic acid skeleton **11**. The synthesis of **11** represents the first stereospecific synthesis of the marasmic acid skeleton.

To proceed further toward the ultimate goal of the natural product, some method for distinguishing the functional groups is necessary. The Diels–Alder adducts of the other dienes **4b–e** with other dienophiles have been investigated and will be the subject of a subsequent report.

Experimental Section

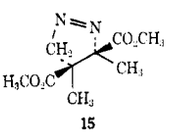
Infrared spectra were recorded on Beckman IR-8, IR-8a, and IR-18a spectrophotometers. Ultraviolet spectra were taken in 95% ethanol solution on a Bausch and Lomb Spectronic 505 spectrometer. Pmr spectra at 60 MHz were taken in dilute CCl_4 solution with internal TMS standard and 500-Hz sweep unless otherwise specified. Mass spectra were obtained on a Consolidated Electrodynamic Corp. 21-110 high-resolution spectrometer. Melting and boiling points were uncorrected. Microanalyses were obtained from Elek Microanalytical Lab-

(14) For a review see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).

(15) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p 39.

(16) Subsequent to its preparation in this laboratory, E. Vogel, *et al.*, *Tetrahedron Lett.*, 1941 (1970), reported the identical synthesis of **14**.

(17) The stereochemistry of compound **10** was deduced by a study of the lanthanide shifted nmr spectra of compound **10**, compound **13**, and reference compound **15**. See S. R. Wilson and R. B. Turner, *Chem. Commun.*, in press, and ref 18.



(18) S. R. Wilson, Ph.D. Thesis, Rice University, Houston, Tex., 1972. (See Scheme I.)

oratory, Harbor City, Calif. Thin layer chromatography employed Brinkman precoated silica gel F-254 plates.

Preparation of Compound (4a).—A benzene solution (50 ml) of 3.03 g of 4,4-dimethyl-1-cyclopentenyl-1-carboxaldehyde (**5**)[18] and 10.6 g of $Ph_3PCHCOOCH_3$ (prepared by the method of Zeller[11]) was refluxed overnight under nitrogen. The benzene was evaporated on a Rotavap and 50 ml of petroleum ether (bp 30–60°) was added. Stirring for about 10 min caused precipitation and crystallization of the Ph_3PO. The supernatant was filtered through a short column (30 g) of activity I Al_2O_3 and distilled to yield 3.92 g (87%) of diene **35**: bp 74–76° (0.5 mm); ir (neat) 1727, 1639 cm^{-1}; nmr δ 1.13 (6 H, s), 2.20 (4 H, s), 3.65 (3 H, s), 5.73 (1 H, d, J = 16 Hz), 6.17 (1 H, m), 7.49 (1 H, d, J = 16 Hz); uv λ_{max} 270 nm (ϵ 25,200); m/e 180 (P). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 9.07.

Preparation of Compound 4b.—Diene **4a** (3.18 g) was refluxed with 0.71 g of NaOH in 75 ml of water under nitrogen for 2 hr. The reaction mixture was then cooled to room temperature, acidified to pH 2 with concentrated HCl, and extracted with ether. Evaporation of the ether gave 2.26 g (95%) of acid **4b**, mp 119–125°. Recrystallization from ether gave the analytical sample: mp 126–128°; ir ($CHCl_3$) 2500–3400 (broad), 1680 cm^{-1}; nmr δ 1.13 (6 H, s), 2.32 (4 H, s), 5.72 (1 H, d, J = 15 Hz), 6.12 (1 H, m), 7.68 (1 H, d, J = 15 Hz), 10.90 (1 H, s); m/e 166 (P). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.93; H, 8.48.

Preparation of Compound 4c.—To a solution of 8.25 g of distilled diene **4a** in 30 ml of dry benzene at room temperature was added 137 ml of a 0.67 *M* diisobutylaluminum hydride (DIBAL-H, Texas Alkyls). The mixture was stirred for 2 hr and then 15 ml of 10% H_2SO_4 was added and the reaction mixture was extracted with ether. The organic layer was washed with water, twice with saturated $NaHCO_3$, and once with brine and dried over $CaSO_4$. Evaporation gave an oil which distilled at bp 69–75° (0.2 mm) to give 5.94 g (86% yield): ir (neat) 3125 cm^{-1}; nmr δ 1.08 (6 H, s), 2.18 (4 H, s), 3.2 (1 H, broad), 4.03 (2 H, d, J = 5 Hz), 5.3 (1 H, d, J = 14 Hz), 5.45 (1 H, m), 6.2 (1 H, d, J = 14 Hz); uv λ_{max} 233 nm (ϵ 3600); m/e 152 (P). This compound was somewhat sensitive and was analyzed as the 3,5-dinitrobenzoate (see compound **4e**).

Preparation of Compound 4d.—A solution of 392 mg of compound **4c** and 370 mg of PhCOCl (10% excess) in 5 ml of dry pyridine was stirred at room temperature overnight. The dark reaction mixture was poured into 150 ml of 1 *N* HCl and extracted twice with ether. The ether was washed with water, saturated $NaHCO_3$, and brine, and subsequently dried over $MgSO_4$ and evaporated to yield an oil. Thin layer chromatography (petroleum ether) gave 300 mg of **4d** (45% yield). For analysis the ester was evaporatively distilled (bath temperature 140°) at 0.1 mm: ir (neat) 1712 cm^{-1}; nmr δ 1.15 (6 H, s), 2.25 (4 H, s), 4.81 (2 H, d, J = 5 Hz), 5.2–5.8 (2 H, m), 6.51 (1 H, d, J = 16 Hz), 7.4 (3 H, m), 7.9 (2 H, m); m/e 256 (P). *Anal.* Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.22; H, 7.62.

Preparation of Compound 4e.—To a solution of 5.13 g of distilled compound **4c** in 50 ml of dry pyridine stirred and cooled was added 8.7 g (20% excess) of 3,5-dinitrobenzoyl chloride. The mixture was stirred overnight at room temperature. The reaction mixture was then poured into 1 l. of 1 *N* HCl and extracted three times with 50-ml portions of chloroform. The chloroform was washed with water, saturated $NaHCO_3$, and brine and dried. Evaporation gave 11.52 g (99%) of a solid, crystalline mass, mp 70–80°. Recrystallization from ether–petroleum ether gave 9.8 g of crystals: mp 79–84°; ir ($CHCl_3$) 3090, 1725, 1540, 1340 cm^{-1}; nmr δ 1.14 (6 H, s), 2.30 (4 H, s), 5.02 (2 H, d, J = 5 Hz), 5.5–6.0 (2 H, m), 6.68 (1 H, d, J = 16.5 Hz), 10.2 (3 H, s); m/e 346 (P). *Anal.* Calcd for $C_{17}H_{18}O_6N_2$: C, 58.96; H, 5.24. Found: C, 58.43; H, 5.42.

Preparation of Compound 7.—A mixture of 1.02 g of dimethyl acetylenedicarboxylate and diene **4a** (1.18 g) was placed in a glass tube, frozen and thawed several times under vacuum, and then sealed. The tube was heated in an oil bath maintained at about 60° for 2 weeks. At the end of this time the tube was opened and its contents were transferred to a 50-ml flask. Heating under vacuum for 2 additional hr at about 75° removed any excess acetylene dicarboxylate. The nmr showed almost pure **7** (2.01 g) with no trace of **8** or **9**. Also no trace of the long-wave absorptions of either **8** or **9** was seen in the uv. Tlc showed a single spot at R_f 0.29 (9:1 benzene–ethyl acetate). Attempted crystallization at −78° in petroleum ether gave crystals which melted below 0°: ir (neat) 1735, 1630 cm^{-1}; nmr δ 1.07 (3 H, s), 1.13 (3 H, s), 1.4–1.8 (2 H, ABX m), 2.17 (2 H, m), 3.2 (1 H, m), 3.68 (6, H, s), 3.74 (3 H, s), 3.80 (1 H, s), 5.30 (1 H, m); mass spectrum m/e 173 (19), 145 (19), 129 (23), 128 (23), 105 (17), 59 (95); uv λ_{sh} 264 nm (ϵ 1700). *Anal.* Calcd for $C_{17}H_{22}O_6$: mol wt, 322.14. Found: mol wt, 322.10 ± 0.04.

Preparation of Compounds 8 and 9.—Diene **4a** (1.8 g), dimethyl acetylenedicarboxylate (1.42 g), and a few crystals of pyrogallol were heated at 100° for 3 days under a nitrogen stream. A mixture of about 40% **9** and 60% **8** resulted. A 370-mg portion of this mixture was separated by tlc. Developing with 9:1 benzene–ethyl acetate showed bands at R_f 0.32 and 0.35. Collection of the first band gave after recrystallization 17 mg of **9**: mp 90–93°; ir ($CHCl_3$) 1725 cm^{-1}; nmr δ 1.15 (6 H, s), 2.78 (2 H, s), 2.98 (2 H, s), 3.87 (6 H, s), 3.92 (3 H, s), 7.82 (1 H, s); uv λ_{max} 294 nm (ϵ 1800); m/e 320 (P). Collection of the second band gave 40 mg of compound **8**: mp 71–72° from ether–petroleum ether; ir ($CHCl_3$) 1740, 1736, 1720 cm^{-1}; nmr δ 1.02 (3 H, s), 1.14 (3 H, s), 2.30 (4 H, broad s), 3.22 (2 H, broad s), 3.68 (6 H, s), 3.73 (3 H, s), 6.84 (1 H, m); uv λ_{max} 301 nm (ϵ 10,900); m/e 322 (P). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.43; H, 6.85.

Preparation of Compound 10.—A solution of 2.01 g of freshly prepared compound **7** was allowed to contact a tenfold excess of diazomethane in ether (about 1 *M*) for 11 days at room temperature. The ether–diazomethane was evaporated and replenished twice in this period. On the 11th day, the ether and excess diazomethane were evaporated and 25 ml of ether was added. On cooling 1.72 g of crude crystals were obtained, mp 108–116°. Recrystallization from a small volume of ether gave 1.35 g of crystals, mp 130–131°, N_2 evolution, in a yield of 60%. Preparative tlc (8:2 benzene–ethyl acetate) of the mother liquor gave an additional 372 mg of pyrazoline **10** (15%, R_f 0.39) and 330 mg of compound **9** (20%, R_f 0.54): ir ($CHCl_3$) 1740, 1562 cm^{-1}; nmr δ 1.02 (3 H, s), 1.08 (3 H, s), 1.3–1.9 (2 H, ABX), 2.2 (2 H, m), 3.15 (1 H, d, J = 11 Hz), 3.58 (3 H, s), 3.74 (3 H, s), 3.82 (3 H, s), 4.98 (2 H, AB q, J = 19 Hz, $\delta_A - \delta_B$ = 30 Hz), 5.81 (1 H, m); uv λ_{max} 220 nm (ϵ 5400); λ_{max} 324 nm (ϵ 135). *Anal.* Calcd for $C_{18}H_{24}O_8N_2$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.10; H, 6.53; N, 7.46.

Preparation of Compound 11.—A solution of 471 mg of pyrazoline **10** in 50 ml of dry ether was degassed at −78° under vacuum for 30 min and then irradiated with a high-pressure mercury arc (450 W Hanovia lamp) for 2 hr at 0–5°. Evaporation of the ether gave 466 mg of an oil whose nmr showed nearly pure cyclopropane (**11**). Crystallization from petroleum ether gave five crops of needles, mp 49–52°, 76% yield. Four recrystallizations from petroleum ether gave the analytical sample: mp 55–56°; ir (neat) 1740 cm^{-1}; nmr δ 1.02 (3 H, s), 1.05 (3 H, s), 1.1–1.9 (4 H, m), 2.17 (3 H, m), 2.75 (1 H, m), 3.68 (3 H, s), 3.69 (3 H, s), 3.72 (3 H, s), 5.95 (1 H, m). *Anal.* Calcd for $C_{18}H_{24}O_6$; mol wt, 336.157; C, 64.27; H, 7.19. Found: mol wt, 336.158; C, 63.90; H, 7.12.

Preparation of Compound 12.—A 1-l. Parr pressure reactor was cooled in Dry Ice–acetone to about −20° and about 50–75 ml of butadiene was condensed. Dimethyl acetylenedicarboxylate (82 g, 0.58 mol), 200 ml of benzene, and 2 g of pyrogallol were added. The bomb was sealed and the reaction mixture was stirred at room temperature for 6 days. Excess butadiene was vented and the benzene was evaporated. The residual oil distilled at 80–85° (0.2 mm) to give 59 g of compound **12** (52% yield): ir (near) 1724, 1645 cm^{-1}; nmr δ 3.1 (4 H, s), 3.83 (6 H, s), 5.92 (2 H, s); m/e 196 (P).

Preparation of Compound 13.—Compound **12** (1.92 g) was dissolved in about 50 ml of ether, and 150 ml of diazomethane solution (containing about 1 g of diazomethane) was added. The flask was sealed with a cork and kept at room temperature for 5 days. Then the ether and excess of diazomethane was evaporated on a steam bath and 150 ml more diazomethane solution was added. After another 5 days at room temperature the excess diazomethane and ether were evaporated to yield 2.11 g of an oil which was by nmr 85% pyrazoline **13**. Thin layer chromatography developing with 9:1 benzene–ethyl acetate gave 450 mg of crystalline **13**, mp 65–72°. Recrystallization from ether gave a sample: mp 74–75°; ir ($CHCl_3$) 1748, 1555 (weak, and 1580 cm^{-1} (weak); nmr δ 2.2–3.1 (4 H, m), 3.60 (3 H, s), 3.67 (3 H, s), 4.75 (2 H, AB qt J = 18 Hz, $\delta_A - \delta_B$ = 44 Hz), 5.78 (2 H, m).

Preparation of Compound 14.—Compound **13** was injected into the vpc (injection port 240°; 6 ft × 0.375 in. Carbowax 20 M at 220°). This showed one peak which was collected and identified as **14**. Alternatively, compound **13** could be irradiated through Pyrex as a dilute ether soluton to give the cyclopropane in quantitative yield.

Registry No.—**4a**, 40447-60-7; **4b**, 40447-61-8; **4c**, 40447-62-9; **4d**, 40447-63-0; **4e**, 40447-64-1; **5**, 38312-94-6; **7**, 40447-66-3; **8**, 40447-67-4; **9**, 40447-68-5; **10**, 40447-69-6; **11**, 40447-70-9; **12**, 14309-54-7; **13**, 40447-72-1; 3,5-dinitrobenzoyl chloride, 99-33-2; dimethyl acetylenedicarboxylate.

Models for the Pyridine Nucleotide Coenzymes. Synthesis and Properties of Bridged Dinicotinamide Derivatives[1-3]

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A number of dinicotinamide derivatives which are bridged between the 3 and the 5 positions have been prepared from dinicotinoyl chloride and α,ω-diamines. A special high-dilution technique involving introduction of reagents into the reaction flask by means of syringe pumps was employed which was superior to the use of constant-rate addition funnels. Models for coenzyme–substrate complexes in which a carbonyl group or alcohol group in the bridge is in close proximity to the 4 position of a dihydropyridine or of a pyridinium salt, respectively, have been prepared. Certain of the bridged derivatives show enhanced reactivity toward silver nitrate and protons which may be a function of the strain introduced into the pyridine ring. No evidence was obtained either for intramolecular hydrogen transfer from the dihydropyridine to the proximate carbonyl group, or for the transfer of hydride ion from the alcohol group to the pyridinium ring. Spectroscopic data, however, indicated addition of alkoxide ion in the bridge to the charged pyridine ring.

Proximity and orientation effects are presumed to be important factors in accounting for the catalytic power of enzymes.[4] The enzyme positions coenzyme and substrate in close proximity so that collisions between the reactants are more frequent. The enzyme also orients them so that the probability of a collision leading to a reaction is increased. Other factors such as acid–base catalysis, introduction of strain in the reactants, the formation of unstable, covalent intermediates, and the polarity of the microscopic environment also are believed to be important in enzyme catalysis.

The dehydrogenase enzymes catalyze the transfer of hydrogen to and from substrates *via* the pyridine nucleotide coenzymes. Relatively few successful model reactions for these hydrogen transfers have been accomplished in the absence of an enzyme.[5] For the model reduction of ketones or aldehydes by 1-substituted 1,4-dihydronicotinamides (models for the coenzyme), only the reduction of halo ketones,[6] the zinc ion catalyzed reduction of 1,10-phenanthroline-2-carboxaldehyde,[7a] and the reduction of pyridoxal phosphate and analogs by dihydropyridines[7b] appear to proceed in good yield in the absence of enzyme. The hydrogen transfer in the enzymic and nonenzymic reactions occurs *via* the 4 position of the pyridine ring[8] and is a direct transfer between coenzyme (or its model) and substrate,[9] although an indirect mechanism *via* tryptophane may operate in certain enzymic reactions.[10]

Introduction of a carbonyl group or an alcohol group close to the reactive 4 position of models for the pyridine nucleotide coenzymes would be a test of proximity effects. While a number of model systems for hydrogen transfer involving pyridine derivatives have been investigated,[5-7] at the time our work began no model system had been reported in which a carbonyl or alcohol moiety had been fixed in close proximity to the 4 position of the pyridine ring. Recently, the bridged dinicotinamide derivative **1** was prepared (6.6% yield in the cyclization step) and was converted to the bridged alcohol derivative **2**. A deoxy analog, **3**, and its 1-benzyl salt also were reported (6.9% yield in the cyclization step). No evidence for intramolecular hydrogen transfer in **2** was obtained,[11a] but an intramolecular hydrogen transfer to a carbonyl group in *N*-(2,6-dichlorobenzyl)-3-(*o*-formylbenzoyl)-1,4-dihydropyridine has been induced photochemically.[11b] A thermally induced intramolecular hydrogen transfer from a 1,2-dihydropyridine to the vinyl group of an acrylic ester has been proposed to account for transformations of the alkaloid, catharanthine.[11c]

We wish to describe in this paper a better procedure

(1) For complete details, see B. B. Blidner, Ph.D. Thesis, Syracuse University, 1972.

(2) This investigation was supported in part by Public Health Service Research Grant No. AM07770 from the National Institute of Arthritis and Metabolic Diseases.

(3) Reported at Northeast Regional Meeting, American Chemical Society, Buffalo, N. Y., Oct 1971, Abstract No. 80.

(4) Included in orientation effects are "freezing" or "stereopopulation control" and "orbital steering:" D. E. Koshland, Jr., and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 370 (1968); D. R. Storm and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci., U. S.*, **66**, 445 (1970); M. I. Page and W. P. Jencks, *ibid.*, **68**, 1678 (1971); S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166, 9175 (1972).

(5) Model systems have been reviewed by T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 9.

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