Also cytotoxic tests against KB cells in tissue culture tests carried out under the auspices of the National Cancer Institute showed the tetra-*N*-demethylactinomycin to be completely inactive (at 100 μg/ml). Actinomycin D strongly inhibits KB cells (ID_{50}, 0.002 μg/ml).[3c]

Registry No.—**1a**, 35085-42-8; **2**, 33662-26-9; **3b**, 35085-44-0; **4**, 35085-45-1; **5**, 35085-46-2; **6**, 35085-47-3; **7**, 35085-48-4; **8**, 35085-49-5; **9**, 35085-50-8; **10**, 35085-51-9; **12**, 35085-52-0; **13**, 35085-55-3; **14**, 35085-53-1; **15**, 35085-54-2.

Acknowledgment.—The authors thank Dr. David W. Henry for his support and guidance and the following for assistance in analytical areas, including most helpful discussions and interpretations: Dr. David W. Thomas, mass spectra; Dr. Gunther Barth, CD spectra; Dr. Joanne Ingwall, CD spectra and Sephadex column separations; Dr. Lois Durham, nmr spectra; Dr. A. Maxwell and P. Devine for *in vitro* antimicrobial tests; Elizabeth M. McCarthy and Dr. Peter Lim and his staff for various analytical services.

The Solid-State Dehydrogenation of L-1,4-Cyclohexadiene-1-alanine Hydrate to L-Phenylalanine

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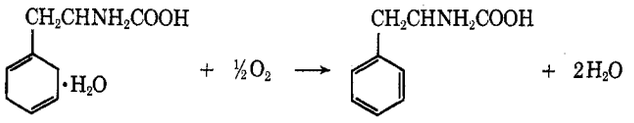
Received January 31, 1972

The solid-state dehydrogenation of L-1,4-cyclohexadiene-1-alanine (I) to phenylalanine is shown to be associated with a hydrated form of I. Crystalline, unhydrated, L-, D-, and DL-1,4-cyclohexadiene-1-alanine products are stable, as are the solid cupric and the newly prepared hydrochloride and sodium salts of I. Dehydrogenation requires molecular oxygen. The reaction is accelerated by reducing the pressure in the presence of desiccant, or, at atmospheric pressure, by heating. It takes place at 100° without racemization. The reaction is interpreted to be a transfer of allylic hydrogen to atmospheric oxygen facilitated by aquation.

Organic reactions known to occur in the solid state include largely cyclization and elimination reactions at temperatures below the melting point and radiation-induced decomposition and polymerization reactions. Uncatalyzed, facile dehydrogenation of hydroaromatics at room temperature or below, to our knowledge, has not been described as a solid-state reaction. This communication describes a novel solid-state reaction occurring at room temperature with no catalyst present, the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine (eq 1). In this facile



solid/gas reaction aquation appears to be a means of lowering the activation energy.[1]

L-1,4-Cyclohexadiene-1-alanine (L-DiHPhe, I) is a new and effective antagonist of phenylalanine; it is obtained simply by a one-step Birch reduction of commercial phenylalanine (Phe).[2-4] Soon after its synthesis and properties had been described, L-DiHPhe was identified in three separate laboratories as a new, naturally occurring inhibitor in bacterial sources.[5] Although L-DiHPhe is stable in solution, as a solid at or below room temperature it was observed sometimes to dehydrogenate to Phe.[2] In contrast, DL-DiHPhe was stable in the solid state as well as in solution, which suggested stereospecificity in the solid-state dehydrogenation. Although a crystallization procedure was provided for preparing L-DiHPhe as a stable solid,[2] the side reaction was expected to limit the usefulness of this Phe antagonist for biological purposes.[6] Thus a systematic investigation of the dehydrogenation of DiHPhe was undertaken.

The dehydrogenation product had been identified originally as Phe on the basis of its chromatographic behavior. The product has now been isolated in crystalline form after preparative chromatography on the amino acid analyzer. Its nmr spectrum, optical rotation, and ability to support the growth of *Escherichia coli* 9723f mutant were the same as those of an authentic sample of L-Phe, thus confirming its identity and establishing that it forms without racemization.

The first reproducible observation of dehydrogenation came when material to be dried had been placed in a high vacuum over phosphorus pentoxide at room temperature. In 3 days, as much as 44% transformation to Phe had occurred, whereas another portion of L-DiHPhe left under atmospheric conditions for the same time had undergone only a small change.[7] L-DiHPhe was then observed to separate into two crystalline forms. Stable prisms formed from a dilute solution in 80% ethanol, and unstable needles formed from a hot, saturated solution in 80% ethanol or from a solution in methanol–ethyl acetate. When dissolved at different concentrations in the same solvent (80%

(1) The conversion of 1,4-cyclohexadiene to benzene is carried out at temperatures of 350–500° [see V. A. Mironov and A. A. Akhrem, *Chem. Abstr.*, **68**, 2607f (1968)].

(2) M. L. Snow, C. Lauinger, and C. Ressler, *J. Org. Chem.*, **33**, 1774 (1968).

(3) B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968).

(4) (a) C. Ressler, D. S. Genghof, C. Lauinger, and M. L. Snow, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 764 (1968); (b) D. S. Genghof, *Can. J. Microbiol.*, **16**, 545 (1970).

(5) Private communications: T. Yamashita, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan, 1968 [see also T. Yamashita, N. Miyairi, K. Kunugita, K. Shimizu, and H. Sakai, *J. Antibiot.*, **23**, 537 (1970)] and G. E. Mallett, Lilly Research Laboratories, 1968. J. P. Scannell, D. L. Pruess, T. C. Demny, T. H. Williams, and A. Stempel, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(6) Amino acid antagonists of phenylalanine suitable for incorporation into peptides have been needed for efforts to modify hormone activity. *p*-Fluorophenylalanine has been used in this way for the synthesis of bradykinin analogs: E. D. Nicolaides, M. K. Craft, and H. A. DeWald, *J. Med. Chem.*, **6**, 524 (1963).

(7) Observed by Miss C. Lauinger.

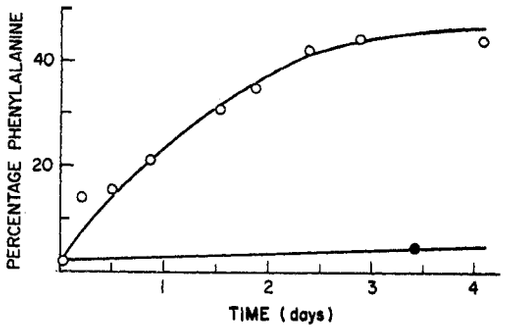


Figure 1.—Pressure dependence of the rate of the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine at 25°: compound allowed to stand over P_2O_5 in a desiccator evacuated to 2 Torr, O—O; compound allowed to stand at 1 atm in a sealed tube, ●—●; and over P_2O_5 in an unevacuated desiccator (not shown) when 6.5% Phe formed (see "Kinetics of Dehydrogenation").

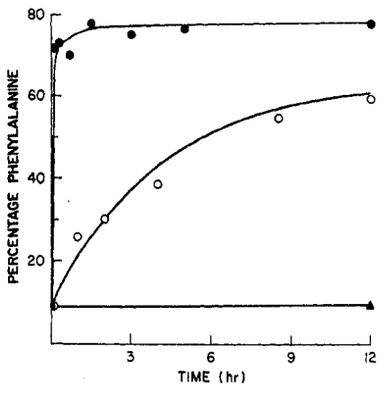


Figure 2.—Temperature dependence of the rate of the dehydrogenation of L-1,4-cyclohexadiene-1-alanine hydrate to L-phenylalanine at atmospheric pressure: 25°, ▲—▲; 60°, O—O; 100°, ●—● (see "Kinetics of Dehydrogenation").

ethanol) and recrystallized, either form could be converted into the other and, in so doing, could adopt the stability characteristic of the new form. Both forms had essentially identical ir spectra and remained stable in 0.2% aqueous solution (5 hr, 100°), suggesting that these were allotropic crystalline forms having different reactivities.[8]

Elemental analysis of the unstable crystalline form of L-DiHPhe indicated that it was a hydrate. Nuclear magnetic resonance spectra in D_2O, which showed an enhanced HDO peak of the expected intensity for the needles but for both forms were otherwise identical, supported this conclusion.

Figure 1 shows the kinetics of dehydrogenation of L-DiHPhe hydrate under reduced pressure and in the presence of desiccant. Dehydrogenation at atmospheric pressure could be accelerated markedly by heating. After 2 hr at 60°, the product contained 30% Phe; after 10 min at 100° the per cent of Phe was 70% (Figure 2). Rates were determined by automatic amino acid analysis.[9]

The stability of various other preparations was then examined by heating several milligrams of solid material in a test tube at 100° for 5 or 8 hr[10] or by placing it over P_2O_5 in an evacuated deisscator for 3.5 days (Table I). The copper complex of L-DiHPhe, which is stable under prolonged storage,[2] was also highly stable when heated or placed in a vacuum. The newly prepared recrystallized hydrochloride and the sodium salt obtained by titration with 1 equiv of 1 *N* NaOH were also much more stable than the hydrate. Unhydrated L-DiHPhe was stable both when heated and under reduced pressure. Even when unhydrated L-DiHPhe was heated in a small, sealed tube in the presence of 0.5–1 part (4.8–9.3 equiv) of added water, less than 1% dehydrogenation resulted, thus showing that for effective dehydrogenation water must be bound intramolecularly in L-DiHPhe.

D-DiHPhe, likewise, crystallized into an unstable form and a stable unhydrated form. Since DL-DiHPhe was known to be stable, equal amounts of the unstable forms of L- and D-DiHPhe were dissolved in water and the solution was concentrated to dryness. On being heated, the residue increased in Phe content from 4.4% to only 7.4%. When recrystallized and then heated, the residue increased from 1.3% to only 2.3% Phe. Originally, DL-DiHPhe had been isolated directly from the Birch reduction mixture of DL-Phe by washing with water to remove salts, whereas L-DiHPhe, because of its greater solubility, had been isolated *via* its copper chelate.[2] L-DiHPhe, therefore, was isolated directly, and DL-DiHPhe was now isolated *via* its copper chelate; their stability characteristics, however, remained unchanged. These experiments were carried out before the unstable form of L-DiHPhe was identified as a hydrate and helped rule out the possibility that an impurity present only in L- and D-DiHPhe was responsible for the dehydrogenation. The stereospecificity of the dehydrogenation is only apparent; it may be accounted for by the observation that, in contrast to the L isomer, DL-DiHPhe does not readily form a molecular hydrate.

When solid samples of L-DiHPhe hydrate were well equilibrated with N_2 gas in sealed, dry ampoules before being heated for 4 hr at 100°, the content of Phe rose from 1% to only 2.7% whereas with O_2 gas the Phe content rose to 63%. Under the same conditions, moreover, DiHPhe or DiHPhe hydrate in 0.2% aqueous solutions saturated with O_2 gas increased in Phe content from 3.3% to less than 5%. Thus atmospheric oxygen, as well as water of hydration, participates in the solid-state dehydrogenation of I.

Repeated analysis showed 0.75 equiv of water to be bound as the hydrate. Since the maximum extent of dehydrogenation on heating has been near 75%, one might speculate that the water of hydration participates stoichiometrically in the dehydrogenation.[11] So far, all attempts to desiccate L-DiHPhe hydrate have

(8) For a discussion of this problem, see H. Morawetz, *Science*, **152**, 705 (1966).

(9) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(10) These experiments were carried out before determination of the dehydrogenation kinetics. Heating for 30–60 min should be adequate.

(11) A possible role for the peroxy radical in the dehydrogenation of the hydrate was investigated. L- and DL-DiHPhe as well as L-DiHPhe hydrate, representing both stable and unstable compounds, and the dehydrogenation mixture all had detectable amounts of peroxide (1–3%), as determined by I_2–thiosulfate titrimetry: V. R. Kokatnur and M. Jelling, *J. Amer. Chem. Soc.*, **63**, 1432 (1941). One sample of L-DiHPhe hydrate that had been left in air for 2 months, with occasional evacuation, had 64% Phe and close to 10% peroxide. Peroxide was not detected in cyclohexadiene, hydroquinone, L-3,4-dihydroxyPhe, or L-Phe. 2,6-Di-*tert*-butyl-4-methylphenol, *n*-propylgallate, and hydroxyurea (1:10 w/w) added as peroxide scavengers were ineffective in retarding the dehydrogenation occurring under reduced pressure over P_2O_5 of the solid L-DiHPhe hydrate.

TABLE I

SELECTIVE DEHYDROGENATION OF 1,4-CYCLOHEXADIENE-1-ALANINE TO PHENYLALANINE IN THE SOLID STATE

Compd	Untreated		Heated at 100°		Evacuated over P_2O_5 (84 hr at 25°)	
	Phe, %[a]	$[\alpha]_D$[b]	Phe, %[a]	$[\alpha]_D$[b]	Phe, %[a]	$[\alpha]_D$[b]
L-DiHPhe	1.7[c]	−58.6	1.3[d]	−60.1	1.8	−60.6
D-DiHPhe	3.6[e]	+58.5	3.9[d]	+57.9	4.0	+57.5
DL-DiHPhe	1.0		1.4[d]		1.0	
L-DiHPhe·0.75H_2O	2.6[f]	−64.1[g]	78	−36.3[g,h]	46[i]	−49.4[g,i]
D-DiHPhe·0.75H_2O	0.7	+60.8[g]	74	+36.8[g,k]		
L- and D-DiHPhe·0.75H_2O						
Mixed	4.4	+0.1	7.4			
Mixed and recrystallized	1.3	−1.4	2.3		1.4	
L-DiHPhe						
1/2 Cupric salt	0.2		0.8		0.4[l]	
Sodium salt	0.2[m]		5.5			
Hydrochloride	0.2[m]		2.5		1.9	
	3.8		6.9		4.5	

[a] Compounds also contained 2–4% Ene. [b] Observed rotations are in 1 *N* acetic acid, *c* 0.5, unless indicated otherwise. Calculated rotations of treated hydrated samples are based on amino acid and water analyses; for L-Phe, $[\alpha]_D$ −34.5°[15] was used; for L- and D-DiHPhe, $[\alpha]_D$ of starting DiHPhe hydrate was corrected for content of Phe, Ene, and water; for Ene, $[\alpha]_D$ of DiHPhe was used. [c] After storage for 4 years at 5°, Phe content was 2.5%. [d] Heated for 5 hr; others, for 8 hr. [e] *Anal.* Calcd for $C_9H_{13}NO_2$ containing 3.6% Phe and 2.1% Ene: C, 64.3; H, 7.82; N, 8.38. Found: C, 64.5; H, 7.9; N, 8.33. [f] After storage for 4 years at 5°, Phe content was 25%. [g] Rotation in water, *c* 0.5–1.0. [h] Calcd $[\alpha]_D$ −35.8°. [i] A portion standing simultaneously at atmospheric pressure contained 4.6% Phe. [j] Calcd $[\alpha]_D$ −49°. [k] Calcd $[\alpha]_D$ +35.6°. [l] After 7 months at 5°, Phe content was unchanged. [m] Phe content in starting DiHPhe hydrate.

resulted in dehydrogenation.[12] Moreover, little dehydrogenation of the hydrate occurred in a vacuum when the P_2O_5 was omitted from the desiccator. Perhaps the lattice water tends to solubilize oxygen within or at the surface of the crystal by hydrogen bonding.[13] Protected by such hydrogen bonding to the water, the oxygen reacts only slowly with the allylic ring hydrogen of L-DiHPhe unless the water is removed or thermal energy is supplied. When the hydrate was equilibrated with N_2 gas before the water of hydration was removed quantitatively, dehydrogenation was considerably less than if no attempts had been made to replace O_2 with N_2 (22% after 1 hr over P_2O_5 at 110° in an evacuated Alderhalden pistol). When heated further in air for 1 hr, however, such desiccated material underwent additional dehydrogenation, the Phe content rising to 78%. Perhaps desiccation of the hydrate leaves L-DiPhe in a conformation that is more susceptible to proton transfer to atmospheric oxygen than is the anhydrous L-DiHPhe obtained directly by crystallization. The described oxidation–reduction reaction can be considered to provide general support for various speculations that structured water plays a role in biological systems.[14]

Experimental Section

Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Water analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., or were carried out as given under "Attempts to Dry DiHPhe·0.75H_2O." Nuclear magnetic resonance spectra were obtained on a Varian A-60A or EM-300 spectrometer. Infrared spectra, melting points, which are corrected, and optical rotations were determined and automatic amino acid analyses were performed as described elsewhere.[2]

Preparation of Compounds.—DL-DiHPhe, L-DiHPhe·1/2Cu, and L-DiHPhe were prepared as described.[2] L-DiHPhe was crystallized from a 2% solution of 80% ethanol; D-DiHPhe and its hydrate were synthesized from D-Phe, $[\alpha]_D$ +33.3° (*c* 2, water) (lit.[15] $[\alpha]_D$ +34.5°), Mann Research Laboratories, N. Y., in the same manner as the L compounds. Analyses and properties are given in Table I.

L-DiHPhe·HCl.[16]—Concentrated HCl (0.83 ml, 10 mequiv) was added to a solution of L-DiHPhe·0.75H_2O (0.5 g, 2.77 mmol, 2.3% Phe) in 10 ml of water, and the solution was concentrated to dryness. The solid residue was crystallized from 95% tetrahydrofuran–ethyl acetate, yield 472 mg (85%), mp 194–198°. For analysis, the material was recrystallized twice, mp 193–195° (very rate dependent), $[\alpha]^{26}_D$ −39.9° (*c* 1, water). It contained 2.5% Phe and 3.7% cyclohexene-1-alanine (Ene).

Anal. Calcd for $C_9H_{14}ClNO_2$: C, 53.1; H, 6.93; N, 6.88; Cl, 17.4. Found: C, 52.9; H, 6.87; N, 7.00; Cl, 17.3.

L-DiHPhe·0.75H_2O.—L-DiHPhe was dissolved in a minimum of warm 80% ethanol and was allowed to crystallize at 25°. The solution was then placed in the cold no longer than overnight. Preparations were examined under the microscope for crystal type and uniformity. The hydrate tended to pack the solution with long needles, in contrast to L-DiHPhe, which had been known to separate well at the bottom of the solution into dense aggregates. The needles were collected and washed first with 80% ethanol, then with absolute ethanol, and finally with ether. The material also could be crystallized from a solution of it in warm methanol containing 1% H_2O and diluted with ethyl acetate. For analysis, samples were dried to constant weight by evacuation at the water pump in the absence of desiccant or under a stream of N_2 gas at atmospheric pressure.

Anal. Of seven samples obtained from L-DiHPhe solutions in 80% ethanol or methanol–ethyl acetate, six had CHN analyses for L-DiHPhe·0.75H_2O and one for L-DiHPhe·H_2O. Calcd for DiHPhe: C, 64.7; H, 7.84; N, 8.38. Calcd for DiHPhe·H_2O: C, 58.4; H, 8.12; N, 7.57. Calcd for DiHPhe·0.75H_2O containing 2.6% Phe and 3.1% Ene: C, 60.1; H, 8.04; N, 7.79. Found: C, 59.9; H, 7.51; N, 7.65. Calcd for DiHPhe·0.75 H_2O containing 1.05% Phe and 3.7% Ene: C, 60.1; H, 8.07; N, 7.78. Found: C, 59.7; H, 7.61; N, 8.02.

Nmr Confirmation of Hydration.—L-DiHPhe in 12.5% solution in D_2O containing 50 μl of NaOD, both 99.7 atom % D, showed after 20 min 3 vinyl H, 6 allylic H, 1 α-CH, and 3.0 HDO; calcd 3 HDO (exchangeable H). L-DiHPhe·0.75H_2O in

(12) A recent report describes an inorganic solid-phase transformation that involves hydration and has some characteristics in common with the dehydrogenation of L-DiHPhe. Isomerization of *trans*-$[Co(NH_3)_4Cl_2]IO_3 \cdot 2H_2O$ to *cis*-$[Co(NH_3)_4Cl_2]IO_3$ is accelerated by heating, and it occurs with samples kept at room temperature in a vacuum over P_2O_5 and on all attempts at desiccation. Moreover, the similar unhydrated trans bromate does not isomerize: H. E. LeMay, Jr., and J. C. Bailar, Jr., *J. Amer. Chem. Soc.*, **89**, 5577 (1967).

(13) In response to a query by a referee, it is noted that the various analytical data for the hydrate can also be reconciled reasonably well with a hemihydrate structure containing 0.125 g-mol O_2.

(14) D. T. Warner, *Annu. Rep. Med. Chem.*, 256 (1969).

(15) A. Meister, "Biochemistry of the Amino Acids," 2nd ed, Academic Press, New York, N. Y., 1965, p 141.

(16) This compound was prepared by Miss L. Diamond.

equimolar solution showed 3 vinyl H, 6 allylic H, 1 α-CH, and 4.4 HDO; calcd 4.5 HDO. Correction was made for the HDO in D_2O–NaOD and for the Phe + Ene content.

Attempts to Dry L-DiHPhe·0.75H_2O.—When heated on a hot block under a stream of H_2 gas at 100°, DiHPhe hydrate lost 3.5% in weight, at 120° 4.7–4.8%, and at 155° 6.9% (Micro-Tech). At 100 and 110° in a vacuum it lost 6.8 and 7.04%, respectively (Schwarzkopf); calcd (cor) for DiHPhe·0.75H_2O: 7.1%. The latter procedure was adopted for the determination of water. Heating at 139° with constant evacuation at 0.05 Torr was unreliable, since some material, which contained Phe and DiHPhe, condensed onto the cool portion of the Abderhalden pistol.

Kinetics of Dehydrogenation.—The timed experiment showing the effect of reduced pressure was carried out by placing 100–200 mg of L-DiHPhe·0.75H_2O in a 30-ml crystallizing dish over P_2O_5 in a desiccator (10-cm diameter) that was evacuated to 2 Torr for 2 min, closed, and then allowed to stand at 25°. At the times indicated in Figure 1, several milligrams were removed and dissolved in water for analysis. The desiccator was reevacuated to 2 Torr and allowed to stand, and the process was repeated. For comparison, one sample was kept at 1 atm in a sealed tube and another sample over P_2O_5 in an unevacuated desiccator.

The timed experiment showing the effect of temperature was conducted by heating 2- to 3-mg samples of L-DiHPhe·0.75H_2O in corked 3-ml test tubes in an oil bath heated to 60 or 100 ± 1.5°. At the times indicated in Figure 2, 1 ml of water was added, and the solutions were kept frozen until placed on the amino acid analyzer.

Isolation of L-Phenylalanine as the Dehydrogenation Product.—In batches of 20–30 mg per test tube, 448 mg of L-DiHPhe hydrate were heated for 5 hr in an oil bath at 100°, with approximately 78% conversion to Phe. Each batch was chromatographed on the amino acid analyzer in system 1.[2] Fractions of 1 ml were collected and analyzed with ninhydrin.[17] Phe, eluting at 69–78 ml, separated from DiHPhe, eluting at 87–92 ml. The combined eluate containing 281 mg of Phe was desalted on a column of 150 ml of Dowex 50 W X8 (H^+) resin, 100–200 mesh.[18] Two recrystallizations from 50% ethanol yielded 130 mg of L-Phe, a homogeneous product on the analyzer, $[\alpha]_D$ −33.6° (*c* 0.85, water) [lit.[15] $[\alpha]_D$ −34.5° (*c* 1, water)]. Its nmr spectrum as the carboxylate ion in D_2O was identical with that of commercial L-Phe. At concentrations of 5, 10, and 15 μg/ml in Anderson's asparagine medium[19] supplemented with 1.5 mg of $FeNH_4SO_4 \cdot 6H_2O$/l., it afforded the same growth for *E. coli* 9723f as did L-Phe.

Registry No.—L-1,4-Cyclohexadiene-1-alanine hydrate, 16055-12-2; L-phenylalanine, 63-91-2; L-DiHPhe·HCl, 32507-80-5.

Acknowledgments.—This work was aided by Grant NS 04316 from the U. S. Public Health Service and by the Muscular Dystrophy Associations of America. The author is indebted to Dr. Dorothy S. Genghof and Mr. Alan Shiffrin for the microbiological comparison, Dr. L. Wilson of Varian Associates and Mrs. Barbara Cottrell for obtaining the nmr spectra, and Miss Christine Lauinger and Miss Lillian Diamond for valuable assistance.

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The Synthesis of Atheroline. A Route to Phenolic Oxoaporphines

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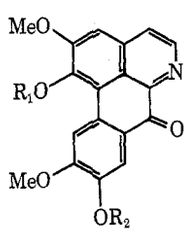
Received March 6, 1972

The alkaloid antheroline (II) has been synthesized. This work represents the first synthesis of a phenolic oxoaporphine base.

The yellow alkaloid atheroline occurs in the bark of *Atherosperma moschatum* L.[1] It was at first assigned the phenolic oxoaporphine structure I,[1] but this formulation was later modified to II as a result of direct comparison of *O*-ethylatheroline (IV) with a series of



I, $R_1 = H; R_2 = Me$
II, $R_1 = Me; R_2 = H$
III, $R_1 = Me; R_2 = COMe$
IV, $R_1 = Me; R_2 = Et$

synthetic trimethoxyethoxyoxoaporphines.[2] We now report the first synthesis of atheroline; this represents also the first synthesis of any phenolic oxoaporphine.

1-(5-Benzyloxy-4-methoxy-2-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (compound V) was prepared starting from 3,4-dimethoxyphenethylamine and 5-benzyloxy-4-methoxy-2-nitrobenzaldehyde[3] (VIII) as described in the literature.[4] Mild oxidation of V with chromic acid in acetic acid afforded the corresponding benzoylisoquinoline (VI) in 53% yield; the aldehyde VIII and the isocarbostyryl[5] IX were obtained as minor products. Dehydrogenation of VI with 10% palladium on charcoal under nitrogen yielded 1-(5-benzyloxy-4-methoxy-2-nitrobenzoyl)-6,7-dimethoxyisoquinoline (VII), mp 168–169°, in 71% yield. The success of this reaction is worthy of note, in view of the survival in the product of both the readily hydrogenolyzed benzyl group and the readily reduced nitro function. A minor proportion of VII (or V) is, in fact, undoubtedly destroyed by acting as the hydrogen acceptor in the dehydrogenation.

A direct one-step conversion of V to VII could also be achieved by heating V with palladium on charcoal in *p*-cymene in the presence of air. In this practical reaction (~50% yield), dehydrogenation of the dihydroisoquinoline system is accompanied by the catalytic oxidation of the activated benzylic methylene group.

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