

Alkaloids of the Papaveraceae. XX. 2,9-Dimethoxy-3-hydroxypavinane, a New Alkaloid from *Argemone munita* subsp. *rotundata*¹

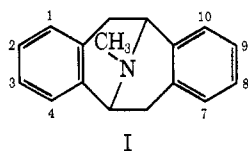
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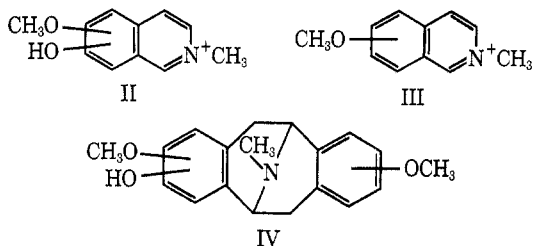
A new alkaloid ($C_{19}H_{21}NO_3$, mp 197–198°, $[\alpha]^{27D} -254^\circ$) was isolated from *Argemone munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. O'wmb. and was shown to be 2,9-dimethoxy-3-hydroxypavinane (I) by total synthesis. The synthesis was accomplished by formation of the Reissert compound from 7-methoxyisoquinoline and 3-methoxy-4-benzyloxybenzyl chloride, conversion to the benzylisoquinoline, N-methylation, reduction to the 1,2-dihydroisoquinoline, and cyclization to I with HCOOH and H_3PO_4 . If the latter three steps were carried out on 1-(4-methoxybenzyl)-6,7-dimethoxyisoquinoline, the final product under the HCOOH and H_3PO_4 conditions was not a pavinane alkaloid, but instead the rearranged product 3-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-N-methylisoquinoline.

From a large-scale extraction of plants of *Argemone munita* subsp. *rotundata* we isolated (see Experimental Section) an alkaloid with the following properties: $C_{19}H_{21}NO_3$ (by combustion analysis and mass spectrum), mp 197–198°, $[\alpha]^{27D} -254^\circ$ (c 1.59, CH_3OH). The high optical rotation and preliminary interpretation of the nmr, uv, and mass spectra indicated that the alkaloid belonged to the pavinane² group (I). Since



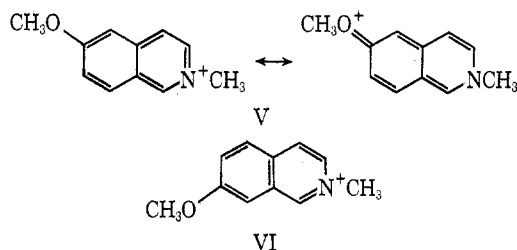
elemental analysis and mass spectrum showed the presence of only three oxygens in the molecule, whereas all previously known pavinanes have contained four oxygens, the isolated alkaloid represented a new compound.

The nmr showed the presence of two methoxy methyl groups and one N-methyl group. The mass spectrum showed intense peaks at m/e 190 and 174, which could (in analogy with previous work³) be assigned structures II and III, respectively. Part structure IV could therefore be assigned to the unknown.



Known natural pavinanes either contain oxygenated substituents only at the 2, 3, 8, and 9 positions (*e.g.*, argemonine, bisnorargemonine) or contain at least one of these substituents at the 4 or 10 position (munitagine, platycerine). In the case of tetrasubstituted derivatives, a clear choice can be made between the two possibilities, since the bridgehead protons of the

central ring appear downfield from the normal position if an oxygenated substituent is in the 4 or 10 position and, in addition, ultraviolet spectra in cyclohexane show characteristic differences³ in the two cases. The uv and nmr spectra of the unknown were characteristic of pavinanes containing substituents only in the 2, 3, 8, and/or 9 positions. Since oxygenated substituents at the 1 and 7 positions are probably unlikely from biogenetic considerations,³ then four possible structures remain for the unknown alkaloid: 2,9-dimethoxy-3-hydroxy-, 2,8-dimethoxy-3-hydroxy-, 3,9-dimethoxy-2-hydroxy-, or 3,8-dimethoxy-2-hydroxypavinane. Differentiation among these possibilities seemed difficult if not impossible without total synthesis. However, two considerations allowed us to at least make a rational choice as to which of the isomers might be the best target for the initial synthesis. First, it was noted that the m/e 190 peak in the mass spectrum was the base peak while the m/e 174 peak was 63% relative intensity. An explanation for the lowered intensity of the m/e 174 peak might reside in its lower stability if it had structure VI rather than V (where charge de-



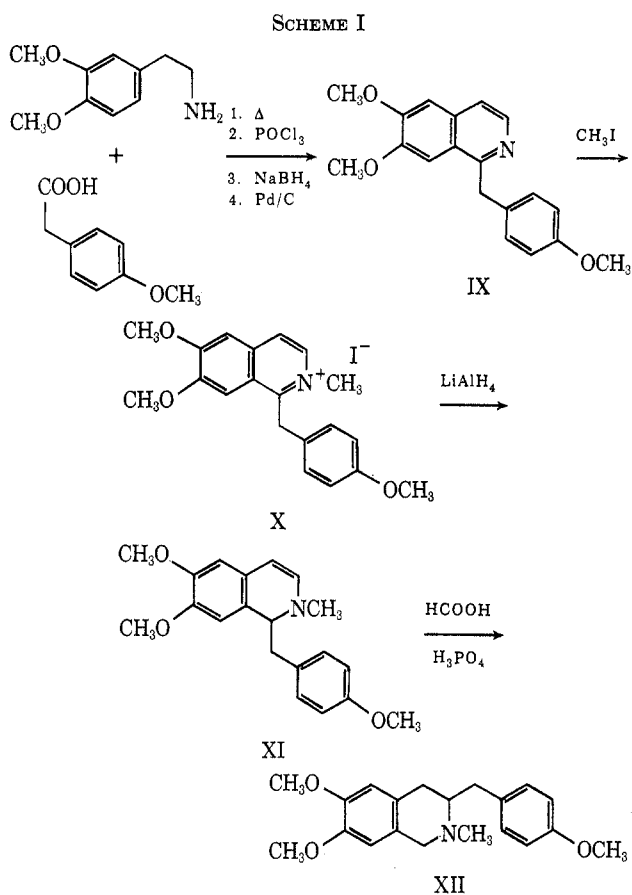
localization is possible). Secondly, some biogenetic arguments can be made. The trisubstituted unknown was isolated as 150 mg of a total alkaloid isolate of 252 g, with bisnorargemonine (2,9-dimethoxy-3,8-dihydroxypavinane) and munitagine (2,9-dimethoxy-3,10-dihydroxypavinane) representing 92% of the alkaloid content.^{3a} If the unknown trisubstituted alkaloid could arise from biosynthetic removal of a phenolic group at position 8 of bisnorargemonine or from position 10 of munitagine, the resultant structure would be VII. The high negative rotation should be reasonable evidence for the absolute configuration indicated, since this is known⁴ for several very similar pavinanes. The alternative would be to propose a complete separate biosynthetic path from a trisub-

(1) Part XIX: F. R. Stermitz, K. A. Larson, and D. K. Kim, *J. Med. Chem.*, in press. This work was supported in part by NIH Research Grants GM 15424 and GM 19234 from the National Institute of General Medical Science.

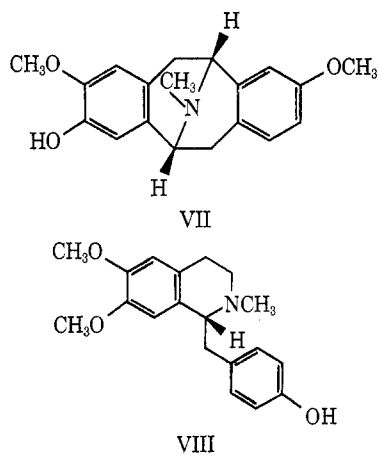
(2) C. H. Chen and T. O. Soine, *J. Pharm. Sci.*, **61**, 55 (1972).

(3) (a) F. R. Stermitz and J. N. Seiber, *J. Org. Chem.*, **31**, 2925 (1966); (b) F. R. Stermitz and K. D. McMurtrey, *ibid.*, **34**, 555 (1969).

(4) A. C. Barker and A. R. Battersby, *J. Chem. Soc. C*, 1317 (1967).



stituted tetrahydrobenzylisoquinoline. We have recently isolated⁵ (+)-armepavine (VIII) as the first

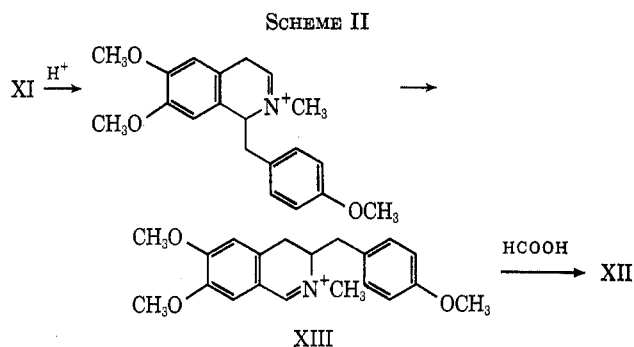


trisubstituted tetrahydrobenzylisoquinoline from an *Argemone* species. The precursor necessary for (+)-armepavine formation would have the proper absolute configuration and oxygenated substituent pattern to be a precursor of VII as well as VIII. Thus, two possible biogeneses and a tenuous suggestion from the mass spectrum each pointed to VII as the best candidate for the structure of the unknown.

Because of the ready availability of starting materials, we elected first to synthesize the completely methylated VII, which could then be compared with the methylated unknown alkaloid. However, the standard pavinane synthesis of Scheme I did not yield a pavinane, but

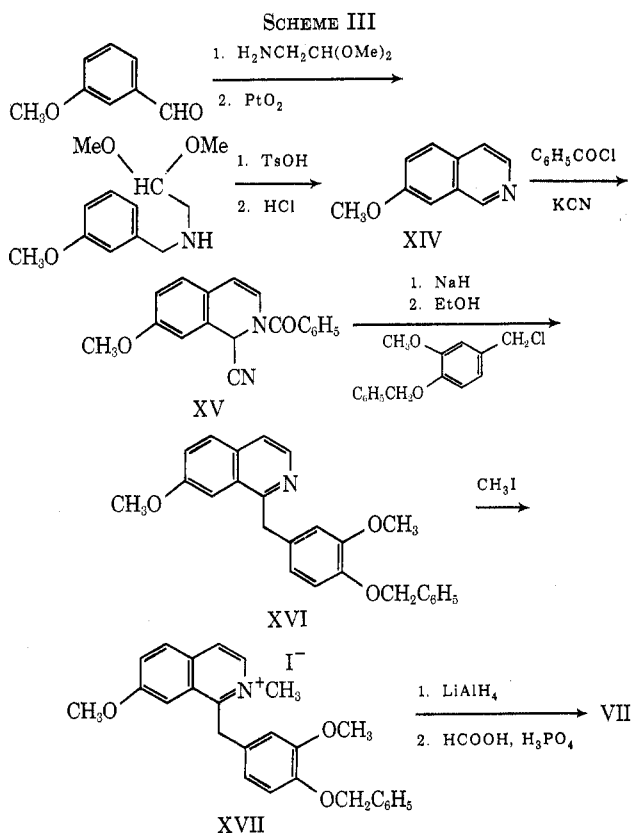
(5) F. R. Stermitz, D. K. Kim, and K. A. Larson, *Phytochemistry*, in press.

instead the rearranged tetrahydrobenzylisoquinoline XII. The formation of XII can be accounted for by Scheme II. Although such a rearrangement has been observed⁶ when 1,2-dihydroisoquinolines similar to XI have been treated with mild acid (acetic acid) conditions, this is the first report of a rearrangement under conditions of the pavinane synthesis. In addition,



rearrangements with mild acid⁶ lead only to the iminium salt XIII, whereas in our case this salt would have been reduced to XII by the HCOOH present. The failure of this attempt to form a pavinane can be attributed to the fact that cyclization must take place meta to a methoxy group and such cyclizations (for example, in the Bischler-Napieralski reaction) are prevented if a methoxy group is in a position meta to the point of cyclization and no ortho or para activating groups are present.

In order to avoid the above problem, we turned to the alternate mode of synthesis given in Scheme III.



(6) J. Knabe, R. Dorr, S. F. Dyke, and R. G. Kinsman, *Tetrahedron Lett.*, 5373 (1972), and references cited therein.

This approach was successful and culminated in the preparation of (\pm)-2,9-dimethoxy-3-hydroxypavinane (VII) which was identical, with the exception of optical rotation and melting points, with the natural alkaloid.

Experimental Section

Isolation.—Dried and powdered, largely above-ground plant parts (125 kg) of *Argemone munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G. B. Owmb., collected 3 miles east of Nephi, Utah, in July 1967, were extracted by our standard³ technique and yielded a total of 252 g (0.22%) of crude alkaloids as a brown solid. This crude solid was crystallized from 500 ml of MeOH to yield 54 g of bisnorargemone. The residue from the mother liquor was dissolved in 1 M H₂SO₄ and this solution was extracted with CHCl₃ after successive pH adjustments to pH 1, 12.5, 11, and 9. At pH 12.5, the solution was extracted with 2 l. of CHCl₃ and evaporation of the CHCl₃ yielded 17 g of crude alkaloids, which proved to be mainly cryptopine and muramine.^{3a} The pH 12.5 aqueous solution was extracted with an additional 2 l. of CHCl₃, but evaporation of this extract yielded a residue (0.5 g) which contained alkaloids other than those of the first pH 12.5 extract. The major alkaloid had *R*_f 0.45 (tlc on Brinkman silica gel F₂₅₄ with 3:2 benzene-methanol as eluting solvent). The crude alkaloid residue was chromatographed on a column of silica gel and yielded (eluting solvent 90:10 CHCl₃-MeOH) 150 mg of pure alkaloid: mp 197–198°; $[\alpha]_D^{25}$ -254° (c 1.59, MeOH); ν_{\max} (KBr disk) 2920, 1625, 1530, 1505, 1460, 1430, 1330, 1260, 1120, 1020, 875 cm⁻¹; nmr (from TMS) δ 2.46 (s, 3 H, NCH₃), 2.35–4.06 (m, 6 H, two ABX-type patterns^{3a} for bridgehead and CH₂ protons), 3.73 (s, 6 H, two OCH₃ groups), 6.45–6.80 (m, 5 H, aromatic H); mass spectrum *m/e* (rel intensity) 311 (55), 190 (100), 174 (63).

Anal. Calcd for C₁₉H₂₁NO₃: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.71; H, 6.59; N, 4.45.

1-(4-Methoxybenzyl)-6,7-dimethoxyisoquinoline (IX).—An equal molar mixture of 25 g of 2-(3,4-dimethoxyphenyl)ethylamine (Aldrich Chemical Co.) and 22.5 g of 4-methoxyphenylacetic acid (Aldrich Chemical Co.) was heated (170–175°) on an oil bath for 3 hr under N₂. The reaction product was cooled and dissolved in benzene and the solution was washed with 1 N HCl, 5% NaHCO₃, and then water. The organic layer was dried and evaporated to yield 41.7 g of *N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide, mp 124–125° after crystallization from ethanol (lit.⁷ mp 126–128°). To a stirred and refluxing solution of 40 g of the amide in 400 ml of dry acetonitrile was added 36 g of POCl₃ over 30 min. The mixture was refluxed under N₂ for 1.5 hr and cooled, and the solvent was evaporated. The residue was dissolved in EtOAc, washed with saturated NaHCO₃ solution, dried, and evaporated to yield 35.8 g of cyclized imine which was used in the next step without further purification.

To a stirred and cooled (0°) solution of 10 g of the above imine in 150 ml of methanol was cautiously added 2.8 g of NaBH₄. After the mixture had stirred for 2 hr at room temperature, the solvent was evaporated and the residue was taken up in water and extracted with CHCl₃. The combined dried CHCl₃ solution was evaporated to give a yellow oil which crystallized from MeOH to yield 8.9 g of 1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, mp 89–90.5°. The HCl salt had mp 183–184.5° (lit.⁸ mp 182°). A mixture of 1 g of this tetrahydroisoquinoline and 75 mg of 10% Pd/C in 50 ml of tetralin was heated (180°) under N₂ for 28 hr. Most of the solvent was distilled under vacuum and the residue was taken up in CHCl₃ and filtered to remove the catalyst. The organic washes were evaporated to give a dark brown oil which readily crystallized from ethanol to yield 805 mg of 1-(4-methoxybenzyl)-6,7-dimethoxyisoquinoline (IX) as a white solid: mp 121.5–122.5°; uv (EtOH) λ_{\max} 320 and 333 nm; nmr (from TMS) δ 3.68 (s, 6 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 4.55 (s, 2 H), 6.72–7.50 (m, 7 H), 8.40 (d, 1 H, *J* = 6 Hz); HCl salt mp 207° dec.

Anal. Calcd for C₁₉H₁₉NO₃: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.46; H, 6.37; N, 4.33.

1-(4-Methoxybenzyl)-6,7-dimethoxyisoquinoline Methiodide (X).—IX (5.0 g) was heated at reflux for 2 hr in 15 ml of MeOH

to which 10 ml of MeI had been added. The solution was evaporated to half its volume and cooled to give a quantitative yield of X, mp 221–223°.

Anal. Calcd for C₂₀H₂₂NO₃I·H₂O: C, 51.18; H, 5.16; N, 2.98. Found: C, 51.36; H, 4.93; N, 2.48.

3-(4-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-*N*-methylisoquinoline (XII).—To a cooled (0°) and stirred dispersion of 1.26 g of X in 100 ml of dry Et₂O was added dropwise a slurry of 0.45 g of LiAlH₄ in 25 ml of dry Et₂O. The slurry was stirred for 4 hr at room temperature and then quenched with 10% aqueous NaOH. The mixture was filtered and washed with ether. The combined organic layers were dried and evaporated to give the dihydro derivative XI (nmr showed a vinyl H doublet at δ 5.23) which was used immediately in the next step. A solution of XI in 3 ml of 85% H₃PO₄ and 7 ml of 90% formic acid was heated at reflux overnight. After it had cooled, the mixture was diluted with 10 ml of H₂O and extracted with ether. The aqueous layer was adjusted to pH 8 and extracted with CHCl₃. The CHCl₃ layers were combined, washed with water, dried, and evaporated to yield a brown oil. This was chromatographed on silica gel to yield 595 mg of XII as a colorless oil which crystallized from ethanol as a white powder: mp 96–97° (picrate mp 176–177°, HCl salt mp 193–194°); nmr (60 MHz, from TMS) δ 2.32–3.26 (m, 8 H, including a singlet at 2.52 for NCH₃), 3.67–3.88 (11 H, 3 OCH₃ absorptions appeared as singlets at δ 3.77, 3.80, and 3.83 but the total integration showed 11 H), 6.55 (s, 2 H, aromatic), 6.84 (d, 2 H, *J*_{ab} = 4.5 Hz), 7.12 (d, 2 H, *J*_{ab} = 4.5 Hz); mass spectrum *m/e* (rel intensity) 206 (100), 204 (15), 121 (8.5).

Anal. Calcd for C₂₀H₂₃NO₃·HCl: C, 66.01; H, 7.20; N, 3.85. Found: C, 66.26; H, 7.07; N, 3.55.

That XII did not have a pavinane structure was evident from the mass spectrum and nmr. Whereas pavinanes exhibit molecular ions at about 50% rel intensity, no molecular ion was observable for XII. The only peak above 15% rel intensity was that at *m/e* 206, while a dimethoxypavinane would exhibit the base peak at *m/e* 204 for the methoxylated ion corresponding to II. The nmr did not show the typical ABX pattern³ of the pavinane central ring protons and included six rather than five aromatic protons. Structure XII is isomeric with a 1-benzyl-tetrahydroisoquinoline, which compounds often lack or show only a small molecular ion. However, in our structure proof⁵ of armepavine from *Argemone turnerae* we had prepared 1-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-*N*-methylisoquinoline, mp 63–64° (lit.⁹ mp 63–64°), by NaBH₄ reduction of X and it was found to be nonidentical with XII. The main spectral key to the structure of XII was the two-proton nmr singlet for the C-1 protons, which could be resolved out from the methoxy region when the nmr was taken at 100 MHz.

7-Methoxyisoquinoline (XIV).—An adaptation of the method of Birch and Jackson¹⁰ was used. Intermediates to XIV were isolate as crudes, but not purified. A mixture of *m*-methoxybenzaldehyde (30 g) and 10% excess aminoacetaldehyde dimethylacetal was heated in benzene at reflux using a Dean-Stark trap until the calculated amount of water collected. Excess aminoacetal was removed by washing with water and distillation *in vacuo*. The residue was reduced to the amine with 1% by weight PtO₂ in ethanol at 50 psi hydrogen in a Parr apparatus. The catalyst was filtered off and the ethanol was removed to yield a residue which was treated with *p*-toluenesulfonyl chloride in pyridine to yield the *N*-tosylate. The *N*-tosylate (30 g) was added to a mixture of 115 ml of 6 N HCl and 400 ml of dioxane and heated at reflux in the dark under N₂ for 6 hr. Work-up¹⁰ of this reaction mixture yielded 10.4 g (81%) of 7-methoxyisoquinoline (XIV), mp 48° (lit.¹⁰ mp 48°).

***N*-Benzoyl-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (XV).**—Benzoyl chloride (0.10 mol) was added dropwise to a stirred solution of 10 g (0.062 mol) of XIV and 0.15 mol of KCN in 75 ml of water at 10°. Stirring was continued until the product separated as a brown solid. This was removed by filtration, washed with water and dilute aqueous HCl, and then crystallized from EtOH to yield 11.9 g (66%) of XV: mp 144–146°; nmr δ 3.83 (s, 3 H, OCH₃), 6.00 (d, 1 H, vinyl, *J* = 4 Hz), 6.53 (d, 1 H, vinyl, *J* = 4 Hz), 6.53 (s, 1 H, C-1 H), 7.50–6.80 (m, 8 H, aromatic).

(9) K. Fujitani and T. Kishimoto, *Yakugaku Zasshi*, **84**, 329 (1964); *Chem. Abstr.*, **61**, 1830d (1965).

(10) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *Tetrahedron Lett.*, **47**, 4789 (1972).

(7) G. J. Kopadia, N. Shah, and R. Highet, *J. Pharm. Sci.*, **53**, 1431 (1964).

(8) H. Kondo and T. Kondo, *J. Pharm. Sci. Jap.*, **48**, 324 (1928).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.76; N, 9.53.

1-(3-Methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline Methiodide (XVII).—The nitrile XV, 11.0 g (0.038 mol), was dissolved in 100 ml of DMF at 0° and was treated under N_2 with a threefold excess of NaH. After 10 min, a twofold excess of 4-benzyloxy-3-methoxybenzyl chloride in 50 ml of DMF was added. The mixture was stirred overnight, excess EtOH was added to destroy remaining NaH, and the mixture was allowed to stir for an additional 24 hr. Benzene and water were added and the benzene layer was separated and washed with water and then with 6 *M* HCl. The acidic layer was made basic with NaOH and extracted with $CHCl_3$. The organic extracts were combined, dried, and evaporated to yield 10.8 g (68%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline (XVI) as a crude brown oil. To this oil was added 50 ml of iodomethane and 50 ml of MeOH and the solution was heated at reflux for 6 hr. The solvent was then removed *in vacuo* to leave a yellow solid, which was recrystallized from ethanol to give 9 g (60%) of 1-(3-methoxy-4-benzyloxybenzyl)-7-methoxyisoquinoline methiodide (XVII), mp 201°.

Anal. Calcd for $C_{26}H_{26}NO_3I$: C, 59.30; H, 4.97; N, 2.67. Found: C, 58.95; H, 4.98; N, 2.35.

(±)-2,9-Dimethoxy-3-hydroxypavinane (VII).—XVII (5 g) was dried and pulverized and then added to a slurry of 1 g of

$LiAlH_4$ in anhydrous ether. The mixture was stirred for 3 hr at room temperature and the excess hydride was decomposed by addition of wet ether followed by a saturated solution of sodium potassium tartrate. The ether layer was separated and evaporated to yield 2.0 g (55%) of the crude 1,2-dihydroisoquinoline as a yellow oil. To this was then added 35 ml of 7:3 $HCOOH-H_3PO_4$ and the solution was heated at reflux for 18 hr. The solution was diluted with water and washed with $CHCl_3$. The aqueous layer was made basic and extracted with $CHCl_3$. The extracts were combined, dried, and evaporated to a crude oil which was 65% VII by nmr and tlc. Column chromatography on Florisil with benzene as eluting solvent yielded pure (±)-2,9-dimethoxy-3-hydroxypavinane (VII), mp 162°, whose ir, nmr, uv, and mass spectra, and tlc R_f values were identical with those of the natural alkaloid.

Registry No.—VII, 41498-94-6; (±)-VII, 41498-95-7; IX, 41498-25-3; IX hydrochloride, 41498-26-4; X, 41498-27-5; XI, 41498-28-6; XII, 41498-29-7; XII picrate, 41498-30-0; XII hydrochloride, 41498-31-1; XIV, 39989-39-4; XV, 41498-33-3; XVI, 41498-34-4; XVII, 41498-35-5; *N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenyl)acetamide, 4078-65-3; 1-(4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, 41498-37-7.

Interconversions of Hexofuranosyl Nucleosides. V. Synthesis and Reexamination of the Structure of 9-(6-Deoxy- α -L-mannofuranosyl)adenine¹

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9-(6-Deoxy- α -L-mannofuranosyl)adenine (**3**) has been prepared by several synthetic procedures and completely structure proofed. It was concluded that the substance previously reported to be **3** really could not have been, based upon the differences in physical properties and the present structure proof. The most successful synthesis required conversion of 6-deoxy-1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-mannofuranose into 6-deoxy-1,2,3,5-tetra-*O*-benzoyl-L-mannofuranose in two steps, conversion of this into the glycosyl chloride with ethereal hydrogen chloride, and condensation of the latter with 6-benzamidochloromercuripurine in hot xylene. Removal of the blocking groups with sodium methoxide and purification *via* a picrate gave an 18% yield of **3**. Other coupling procedures, such as the titanium tetrachloride method, gave rather complex, colored mixtures, which required extensive column chromatography to purify **3**, and consequently lower yields. Attempts to prepare **3** following acetolysis of 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**) resulted in the isolation of 9-(6-deoxy- β -L-glucofuranosyl)adenine (**5**) and 9-(6-deoxy- β -L-mannopyranosyl)adenine (**6**) in addition to **3**. Considerable yields of **5** occurred even under acetolysis reaction conditions that are reportedly not supposed to cause epimerization at C-2. Acetolysis of **4** in 1:1 acetic acid-acetic anhydride with 3% sulfuric acid, followed by nucleoside formation by the titanium tetrachloride procedure, afforded **5**, **3**, and **6** in a ratio of 1.5:2.2:1.0 and acetolysis of **4** in 3:7 acetic acid-acetic anhydride with 5% sulfuric acid changed this ratio to 0.1:1.5:1.0.

The synthesis of hexofuranosyl nucleosides has been a subject of investigation by the author for a number of years.²⁻⁵ Such studies have received occasional impetus from reports in the literature concerning the biological or enzymatic activity of compounds like these.⁶ The purpose of the current investigations was to improve upon the synthesis of hexofuranosyl nucleosides by causing the inversion of configuration at one or more hydroxyl groups of the preformed nucleosides, thereby precluding the necessity of preparing rare sugars to be used in *de novo* synthesis of such compounds.³

In the previous two articles,^{4,5} reasons were presented for the synthesis of 9-(5,6-dideoxy- β -D-erythro-hex-4-enofuranosyl)adenine (**1**) (Chart I). Because of the difficulties encountered in the removal of the isopropylidene blocking group of **2** without complete degradation of the nucleoside, it was thought to be desirable to prepare 9-(6-deoxy- α -L-mannofuranosyl)adenine (**3**, 9- α -L-rhamnofuranosyladenine) in large quantity and, starting from this source, to prepare a derivative of **3** having a blocking group at the 2',3' position which could be more easily removed after the 4',5' double bond was formed. In an attempt to prepare **3** from 6-deoxy-1,5-di-*O*-acetyl-2,3-*O*-isopropylidene-L-mannofuranose (**4**), the latter compound was subjected to acetolysis conditions which are now known to cause epimerization at C-2, and, as a result, two nucleosides were formed from the uncharacterized syrup upon condensation with 6-benzamidochloromercuripurine. The main product was 9-(6-deoxy- β -L-glucofuranosyl)adenine (**5**) and the other was 9-(6-deoxy- α -L-mannopyranosyl)adenine (**6**).⁵ Conditions were sought for the acetolysis of **4** not accompanied by epimerization and

(1) The present work was supported by Grant No. CA13802 from the National Cancer Institute, National Institutes of Health.

(2) (a) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966); (b) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **31**, 1503 (1966); (c) L. M. Lerner, B. D. Kohn, and P. Kohn, *ibid.*, **33**, 1780 (1968); (d) ref 3-5.

(3) L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972); **37**, 473 (1972).

(4) L. M. Lerner, *J. Org. Chem.*, **37**, 477 (1972).

(5) L. M. Lerner, *J. Org. Chem.*, **37**, 4386 (1972).

(6) For examples, see A. Hampton, P. J. Harper, and T. Sasaki, *Biochemistry*, **11**, 4736 (1972); J. F. Henderson, A. R. P. Paterson, I. C. Caldwell, B. Paul, M. C. Chan, and K. F. Lau, *Cancer Chemother. Rep.*, [2] **3**, 71 (1972); I. C. Caldwell and J. F. Henderson, *ibid.*, **2**, 237 (1971); and J. F. Henderson, J. F. Gadd, R. E. A. Palser, and M. Hori, *Can. J. Biochem.*, **48**, 573 (1970).