

Studies on the Chemical Constituents of Rutaceous Plants. LI.<sup>1)</sup>  
Development of a Versatile Method for the Synthesis of  
Antitumor-Active Benzo[c]phenanthridine Alkaloids.  
(3).<sup>1)</sup> Detailed Examination of the Synthesis of  
2-Aryl-1-formamido-1,2,3,4-tetrahydronaphthalene from 2-Aryl-1-tetralone  
Derivatives

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In order to establish a general preparative method for 2-aryl-1-formamido-1,2,3,4-tetrahydronaphthalene derivatives from 2-aryl-1-tetralones, various methods were examined with 6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one as a model compound.

**Keywords**—Robinson method; benzo[c]phenanthridine alkaloid; 2-aryl-1-tetralone; 2-aryl-1-formamido-1,2,3,4-tetrahydronaphthalene; Leuckart reaction; synthesis; geometrical isomer

In the preceding paper,<sup>1b)</sup> we reported the preparation of a number of 2-aryl-1-tetralone derivatives (tetralones) (1) which are key intermediates in the syntheses of antileukemic benzo[c]phenanthridine alkaloids<sup>2)</sup> according to the synthetic sequence developed by Robinson *et al.*<sup>3)</sup> In the synthetic sequence, the tetralone (1) should subsequently be transformed into 2-aryl-1-formamido-1,2,3,4-tetrahydronaphthalenes (formamides) (2) by conversion of the ketonic function to a formamide group. However, since it is well known that this step is one of the major obstacles in this sequence, we carried out a detailed examination of the reported methods [i) direct conversion of the ketonic function into a formamide group by means of the Leuckart reaction<sup>3a,4)</sup> and ii) formylation of 2-aryl-1,2,3,4-tetrahydro-1-naphthylamines (amines) (3) obtained by various reductions (a, reduction with sodium metal in alcohol;<sup>3b,5)</sup> b, reduction with sodium amalgam;<sup>4a)</sup> and c, catalytic hydrogenation over Raney nickel<sup>6)</sup> of 2-aryl-1-tetralone oxime (oxime) (4) derived from the original tetralone (1)] as well as other possible methods with the trimethoxy-tetralone (1a) as a model. In this paper, we describe the results of our examinations.

### 1. Leuckart Reaction of the Tetralone (1)

In 1950, Robinson *et al.*<sup>3a)</sup> applied the Leuckart reaction to the tetralone derivative (1b) and obtained the desired formamide derivative (2b) along with the 3-aryl-1,2-dihydronaphthalene (stilbene) (5b) as a by-product. Later, many research groups<sup>4)</sup> adopted this method for syntheses of benzo[c]phenanthridine alkaloids and related compounds but no one considered the stereochemistry of the resulting formamide (2). However, since the configuration of the formamide (2) might be a dominant factor determining the yield of the Bischler-Napieralski reaction, the following step, we examined this point in detail.

Treatment of the trimethoxy-tetralone (1a) with formamide [HCONH<sub>2</sub>] in formic acid in the presence of ammonium sulfate gave a diastereomeric mixture (2a) of the trimethoxy-

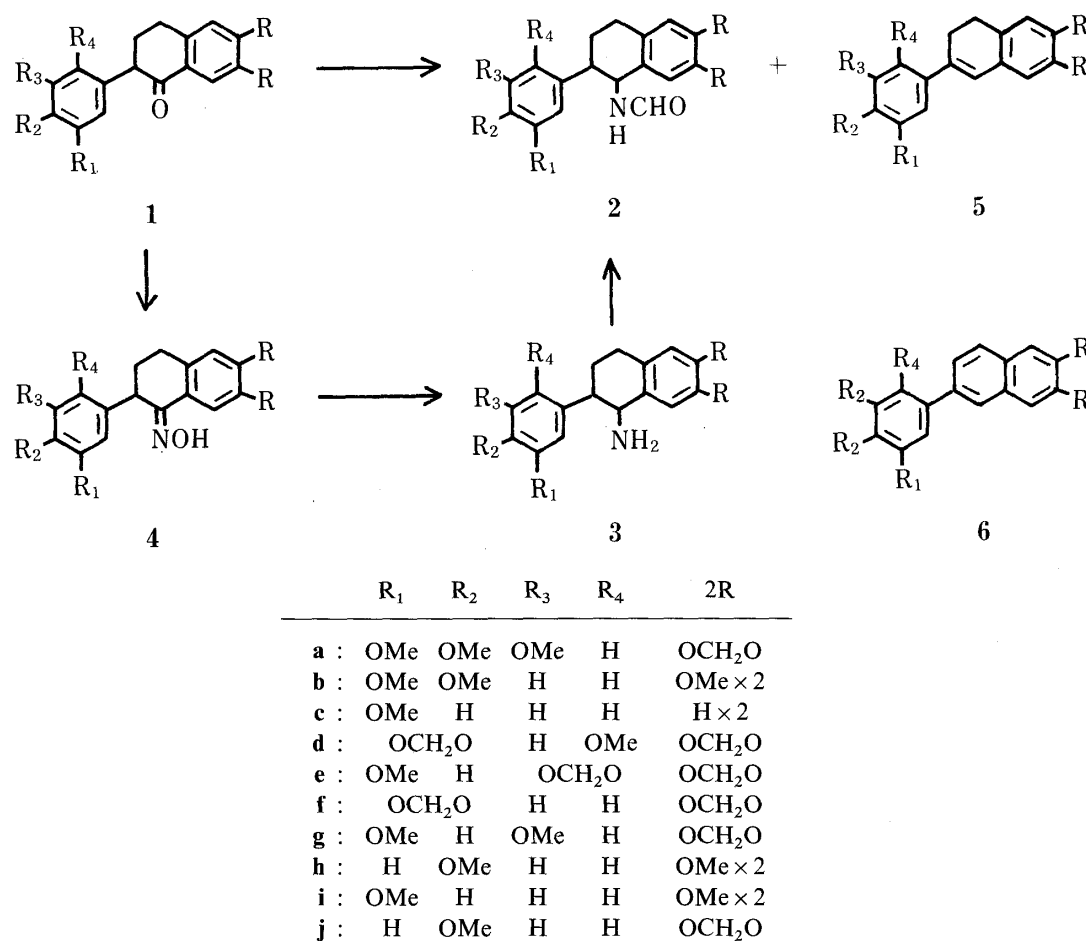


Chart 1

formamides, mp 161—173 °C,<sup>7)</sup> along with the trimethoxy-stilbene (**5a**), mp 120.5—121.5 °C, in 71.4% and 5.1% yields, respectively. In the proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectrum of the diastereomeric mixture (**2a**), the relative intensity of two singlets due to formyl protons at δ 8.15 and 8.02 was in the ratio of 2:1. Careful recrystallization of the mixture (**2a**) from a mixed solvent (chloroform and benzene) gave one component (*trans*-**2a**), mp 191.5—193.5 °C, in 34.6% yield. The mother liquor of recrystallization gave a mixture of the two components in different ratio (*trans*-**2a** : *cis*-**2a** = 3:5). Preparative thin layer chromatography (p-TLC) of the mixture provided *cis*-**2a**, mp 178.5—180.5 °C. In the <sup>1</sup>H-NMR spectrum, each of these pure components shows only one singlet due to a formyl proton at δ 8.15 or 8.02, respectively. Moreover, in the <sup>1</sup>H-NMR spectrum of the former (*trans*-**2a**), the signal due to the proton at the root of the formamide group appears at δ 5.50 as a doublet having a *J* value of 10.0 Hz, while the corresponding signal of the latter (*cis*-**2a**) at δ 5.57 is a doublet having a *J* value of 4.5 Hz, demonstrating that the former is *trans*, while the latter is *cis*. In the <sup>1</sup>H-NMR spectrum, inspection of the relative intensities of formyl signals of the parent Leuckart mixture (**2a**) disclosed that the *trans*- and *cis*-trimethoxy-formamides (*trans*- and *cis*-**2a**) are present in a ratio of 2:1. It should be added here that several other signals were observed collapsed at room temperature even in the <sup>1</sup>H-NMR spectrum of each pure compound (*trans*- or *cis*-**2a**), but became clear-cut when measured at 140 °C. These phenomena may be explicable in terms of restriction of free rotation of the molecule around the single bond between nitrogen and formyl carbon at room temperature.

The formation of the stilbene (**5a**) during the Leuckart reaction provided us a clue for developing a chemical proof of the stereochemical structures. When treated with formic acid

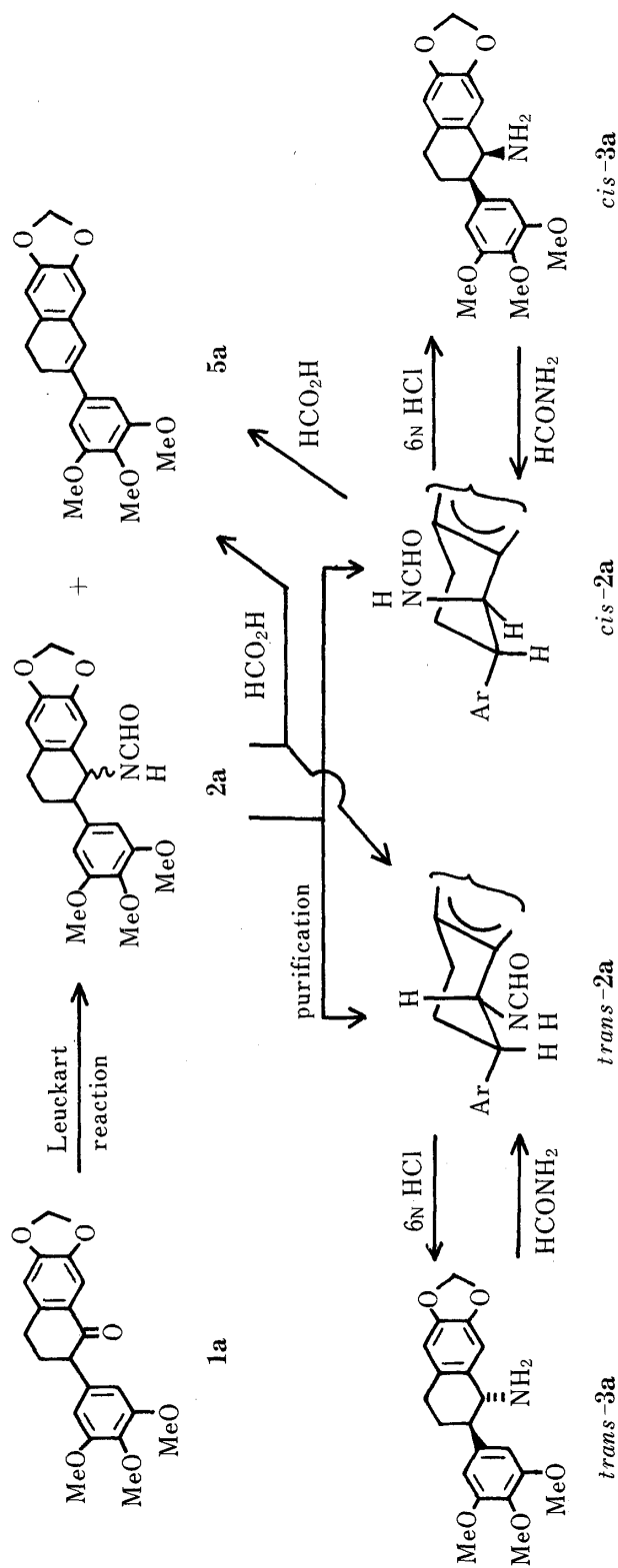


Chart 2

TABLE I. Yields (%) in the Leuckart Reaction of Several Tetralones (1)

Starting tetralone (1)	A diastereomeric mixture of the formamide (2)	The stilbene (5) or the naphthalene (6)
a	71.4	5.1 (5a)
c	58.3	—
d	22.1	9.0 (6d)
e	34.6	—
f	58.9	6.7 (5f)

for 3 h, the pure *cis*-formamide (*cis*-2a) was transformed into the stilbene (5a) in 90% yield, while the pure *trans*-formamide (*trans*-2a) was recovered in 54.3% yield with the formation of the stilbene (5a) in 26.0% yield. The chemical evidence that the *cis*-formamide (*cis*-2a) is more susceptible to formic acid than the *trans*-formamide (*trans*-2a) can be ascribed to the mutual 1,2-diaxial arrangement of the formamide group and the C<sub>2</sub> proton of the *cis*-formamide (*cis*-2a). Furthermore, direct treatment of the Leuckart mixture (2a) under the same conditions gave the pure *trans*-formamide (*trans*-2a) together with the stilbene (5a) in 35.9 and 54.8% yield, respectively, providing a practical procedure for preparation of the pure *trans*-trimethoxy-formamide (*trans*-2a).

On the other hand, surprisingly, treatment of each pure formamide (*trans*- or *cis*-2a) with 6 N hydrochloric acid afforded the *trans*-amine (*trans*-3a), mp 125—126 °C, or the *cis*-amine (*cis*-3a), mp 144—147 °C, as a sole product in 87.2% or 93.6% yield, respectively. These free amines (*trans*- or *cis*-3a) were also reconvertible to the starting formamides (*trans*- or *cis*-2a) by treatment with formamide [HCONH<sub>2</sub>]. It seems that the formation of the *cis*-amine (*cis*-3a) without the stilbene (5a) on treatment of the *cis*-formamide (*cis*-2a) with 6 N hydrochloric acid is in conflict with the chemical finding that the same *cis*-formamide (*cis*-2a) provided the stilbene (5a) when treated with formic acid. However, these results can be reconciled by supposing that the rate of hydrolysis of the *N*-formyl group with 6 N hydrochloric acid is so fast that the  $\beta$ -elimination of a formamide molecule cannot take place.

These experimental results naturally led us to conclude that the *trans*-derivative (*trans*-2) was preferable to the *cis*-derivative (*cis*-2) as the starting formamide in the Bischler-Napieralski reaction in order to minimize the formation of the stilbene (5) as a by-product, because the reaction proceeds through a step in which a cationic center is formed on the carbon carrying the amide group. Consequently, we attempted to find a reaction sequence which would give the *trans*-formamide derivative (*trans*-2) as the main product.

It should be noted here that the Leuckart reaction of the monomethoxy-tetralone (1c) (*vide infra*) gave a mixture of the diastereomeric formamides (2c) without formation of the corresponding stilbene (5c). This observation was consistent with the fact that treatment of the diastereomeric mixture (2c) with formic acid even under refluxing for 10 h did not provide pure *trans*-formamide (*trans*-2c). On the other hand, in our studies on the structural establishment of chelirubine<sup>8)</sup> (7), we had utilized Leuckart reactions of the 2-methoxy-4,5-methylenedioxy- and the 5-methoxy-2,3-methylenedioxy-tetralones (1d and 1e). In these cases, however, the desired formamides (2d and 2e) could be obtained only in poor yields. Moreover, since avicine<sup>9)</sup> (8) was needed for a study of the structure-activity relationship for antileukemic activity in our laboratory, the Leuckart reaction of the 3,4-methylenedioxy-tetralone (avicine-tetralone) (1f) had been examined according to the reported procedure.<sup>4b)</sup> In this case, the desired formamide (2f) was obtained in moderate yield. These experimental results indicated that the yield of the desired formamide (2) in the Leuckart reaction of the

tetralone derivatives (**1**) varied substantially depending on the structures.

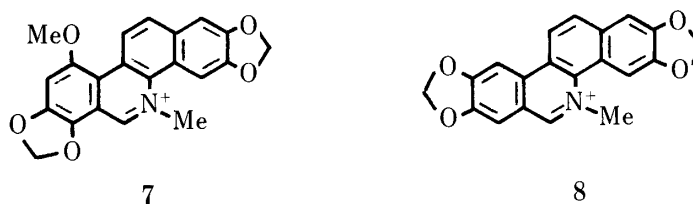


Chart 3

## 2. Reduction of the Oxime (**4**) with Sodium Metal in Ethanol

It is well known that reduction of oximes with sodium metal in alcohol gives the corresponding amines. Originally, in 1937, Robinson *et al.*<sup>3b)</sup> prepared the amine (**3b**) from the corresponding oxime (**4b**) by this method. Moreover, in 1964, Masamune *et al.*<sup>10)</sup> reported the formation of *trans*-2-phenylcyclohexylamine (**9**), a thermodynamically controlled product,<sup>11)</sup> on treatment of 2-phenylcyclohexanone oxime (**10**) with this reagent. More recently, Kametani *et al.*<sup>5)</sup> applied this method to the oxime (**4c**) and reported the formation of the *trans*-amine (*trans*-**3c**) as a sole product.

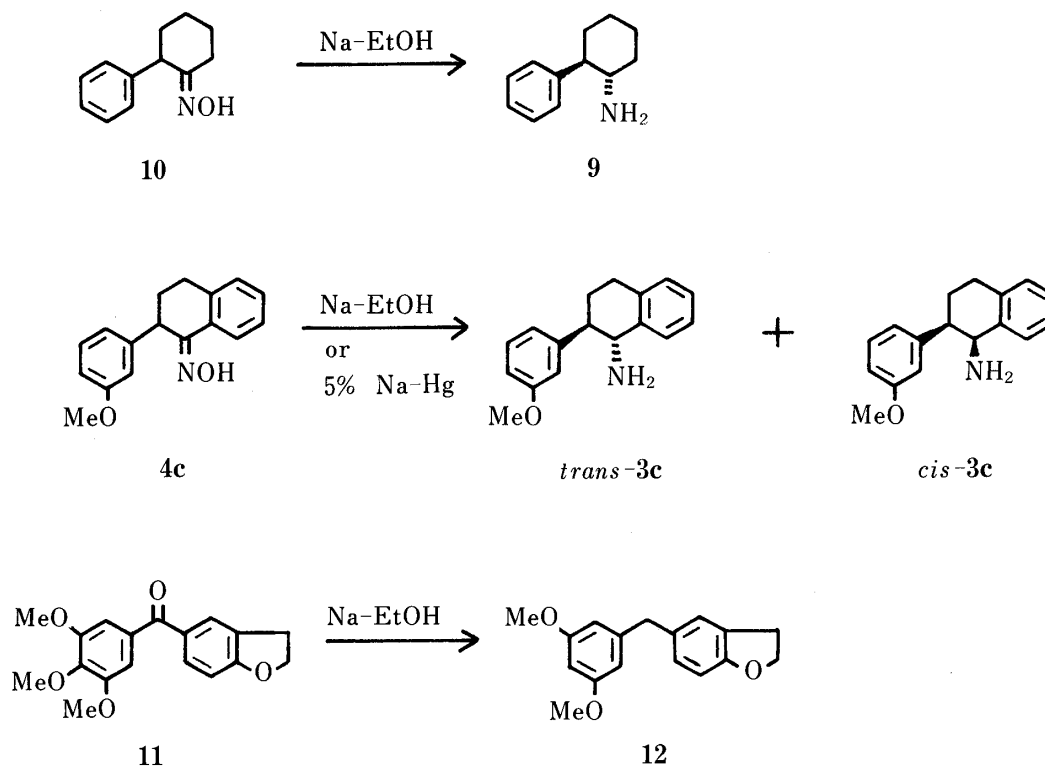
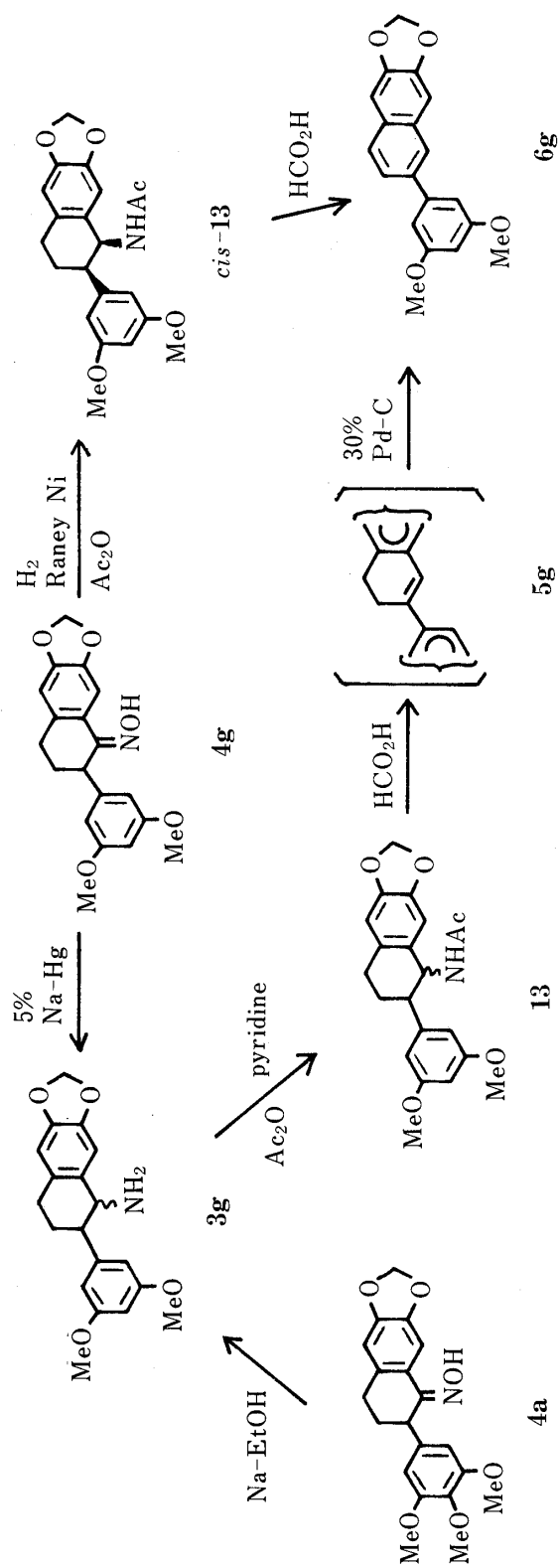


Chart 4

Therefore, we treated the trimethoxy-oxime (**4a**) with sodium metal in ethanol and obtained an oily amine. In the mass spectrum (MS), the amine shows its parent peak at *m/z* 327 instead of *m/z* 357 corresponding to that of the desired trimethoxy-amine product (**3a**), and elemental analysis of the amine hydrochloride, mp 223—226 °C, was consistent with the molecular formula, C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>·HCl, indicating that a methoxy group of the starting trimethoxy-oxime (**4a**) was removed by reduction. There are several reports<sup>12)</sup> on removal of a methoxy group by reduction of a compound bearing a poly-methoxybenzene nucleus with sodium metal in alcohol. For example, in 1908, Kostanecki<sup>12a)</sup> reported that treatment of the 3,4,5-trimethoxybenzoyl compound (**11**) with the same reagent provided the 3,5-dimethoxy



derivative (12). These reported observations suggested that the undefined dimethoxy-amine could be the 3,5-dimethoxy-amine (3g). This presumption was supported by the spectral observation that, in the  $^1\text{H}$ -NMR spectrum, the undefined amine (3g) shows many aromatic proton signals split by a small  $J$  value (*ca.* 1—1.5 Hz) corresponding to a *meta* coupling constant. Moreover, detailed inspection of the general signal pattern of the undefined amine (3g) cast doubt on the view that this might be a mixture of diastereomeric isomer (*vide infra*).

In order to establish the plain structure, the undefined amine (3g) was transformed into the corresponding dimethoxy-stilbene (5g) by acetylation with acetic anhydride in pyridine followed by treatment with formic acid. However, the desired stilbene (5g) was so labile that it underwent air-oxidation to give a mixture of the stilbene derivative (5g) and the fully aromatized product (6g). Therefore, the crude mixture was directly dehydrogenated with 30% palladium-carbon in *p*-cymene without any purification to give the fully aromatized compound (6g) as a sole product. Independently, the reduction of the oxime (4g) prepared from the 3,5-dimethoxy-tetralone<sup>1b)</sup> (1g) with 5% sodium amalgam (*vide infra*) gave a diastereomeric mixture of the amines (3g) which was acetylated with acetic anhydride to give the acetamide (13). The *cis*-derivative (*cis*-13) of the acetamide could be directly prepared by catalytic hydrogenation of the oxime (4g) over Raney nickel in acetic anhydride.<sup>13)</sup> The product (13) was also converted into the corresponding naphthalene derivative (6g) by treatment with formic acid followed by 30% palladium-carbon in *p*-cymene. The naphthalene derivative (6g) was identical with the fully aromatized product (6g) derived from the undefined dimethoxy-amine (3g). This reaction sequence established the plain structure of the undefined amine as the formula (3g).

The undefined oily dimethoxy-amine (3g) was shown to be a mixture of diastereomeric isomers by spectral evidence. In the  $^1\text{H}$ -NMR spectrum, although the two methoxy groups of the 3,5-dimethoxy-amine (3g) in the stereochemically pure products are theoretically equivalent, the signals due to two methoxy groups of the undefined amine (3g) hydrochloride were observed as two 3H singlets at  $\delta$  3.75 and 3.81 instead of a 6H singlet. In addition, the coupling patterns of other signals were observed collapsed to multiplets. These observations allowed us to conclude that the undefined dimethoxy-amine is present as a diastereomeric mixture of 3,5-dimethoxy-amine (*trans*- and *cis*-3g).

At this point, we wondered why the reduction of the trimethoxy-oxime (4a) with sodium metal in alcohol had provided a mixture of diastereomeric products in contrast to Kametani's result. Thus, we attempted to re-examine their experiments. The oxime (4c) prepared according to their description<sup>5)</sup> was treated with sodium metal in ethanol to give an oily amine (3c) as described in their report.<sup>5)</sup> In the  $^1\text{H}$ -NMR spectrum, this oil (3c) shows the signal due to the methine proton ( $\text{C}_1\text{-H}$ ) adjacent to the amine group as a set of three peaks at  $\delta$  4.03, 4.11, and 4.14. These seemed to be composed of two doublets, one doublet ( $\delta$  4.11 and 4.14) having a  $J$  value of 3 Hz and the other doublet having a  $J$  value of 11 Hz or 8 Hz on the assumption that the counterpart of the signal at  $\delta$  4.03 overlapped with either that at  $\delta$  4.11 or that at  $\delta$  4.14. Since the intensity of the former signal is larger than that of the latter, we may conclude that Kametani's amine was also a diastereomeric mixture containing a larger amount of the *cis*-isomer<sup>14)</sup> (*cis*-3c). Although all attempts to separate the mixture (3c) into the components by converting it to formyl, acetyl, and benzoyl derivatives failed, our conclusion was also supported by the fact that, in the  $^1\text{H}$ -NMR spectrum the formyl derivative (2c) shows the formyl proton as two singlets at  $\delta$  7.88 and 8.04.

It should be added here that reduction of the 2-methoxy-4,5-methylenedioxy-oxime (4d) with sodium metal in ethanol also gave a diastereomeric mixture of the desired amine (3d) along with an undefined amine (14) in 21.7% and 5.4% yields, respectively. In the  $^1\text{H}$ -NMR spectrum, the latter (14) shows two methoxy signals at  $\delta$  3.60 and 3.66 and a methylenedioxy signal at  $\delta$  5.94. Although these spectral results demonstrate that one alkoxy bond of the

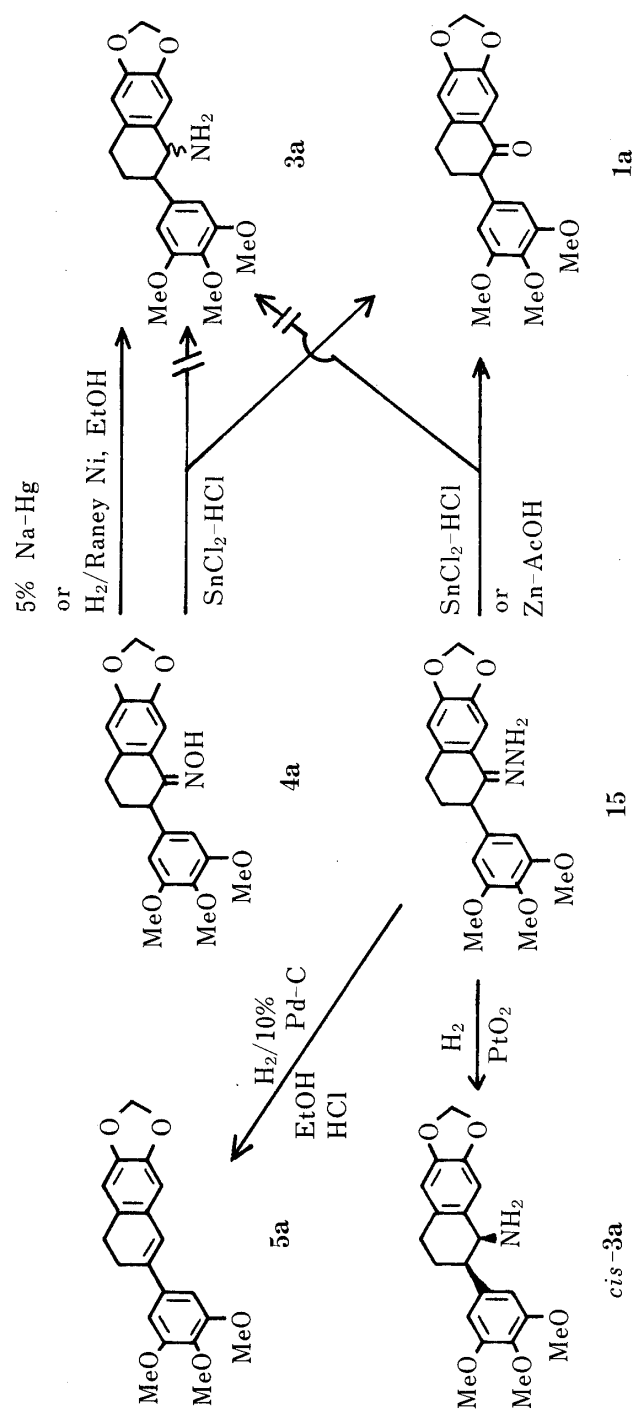


Chart 6

15

*cis*-3a



methylenedioxy group in 2-methoxy-4,5-methylenedioxy-oxime (**4d**) was also reductively cleaved into a methoxy group, the structure of the product (**14**) remains to be solved.

### 3. Reduction of the Oxime (**4**) with Sodium Amalgam

It is also well known that reduction of oximes with sodium amalgam gives a thermodynamically controlled product.<sup>15)</sup> In 1957, Gopinath *et al.*<sup>4a)</sup> prepared the amines (**3h**, **3i**, and **3j**) from the oximes (**4h**, **4i**, and **4j**) with this reagent in relatively good yields, so we applied this method to two oximes (**4a** and **4c**). Reduction of the trimethoxy-oxime (**4a**) with this reagent provided a mixture of diastereomeric products (**3a**). Detailed examination of the <sup>1</sup>H-NMR spectrum of the mixture (**3a**) in comparison with those of the pure amines (*cis*- and *trans*-**3a**) revealed that the product ratio of this mixture was 4 : 3 (*cis*-**3a** : *trans*-**3a**). In the case of the monomethoxy-oxime (**4c**), a diastereomeric mixture of the desired amine (**3c**) was also obtained in good yield. However, as Leuckart reaction of the two tetralones (**1d** and **1e**) resulted in poor yields as described above, we attempted to prepare these formamides (**2d** and **2e**) through this method. Although a suitable formylation procedure for the diastereomeric mixture was required for this purpose, fortunately, formylation of the *cis*- and *trans*-trimethoxy-amines (*cis*- and *trans*-**3a**) with formamide [HCONH<sub>2</sub>] provided the corresponding desired formamide (**2a**) in reasonable yield as described above. Thus, large amounts of these amines (**3d** and **3e**) were prepared by reduction of the corresponding oximes (**4d** and **4e**) with sodium amalgam followed by formylation with formamide [HCONH<sub>2</sub>] for further research. In addition, to aid the structural establishment of the undefined dimethoxy-amine product obtained on the reduction of the trimethoxy-oxime (**4a**) with sodium metal in ethanol (*vide ante*), the 3,5-dimethoxy-amine (**3g**) was also prepared by this method.

### 4. Catalytic Reduction of the Oxime (**4**) over Raney Nickel

On the other hand, we also undertook to obtain the pure *cis*-amine (*cis*-**3**) in better yield in order to compare the Bischler–Napieralski reaction of the pure *cis*-formamide (*cis*-**2**) with that of the pure *trans*-formamide (*trans*-**2**). For this purpose, we carried out catalytic reduction<sup>13)</sup> of the oxime (**4a**) over Raney nickel in ethanol; this procedure gave a diastereomeric mixture of amines (**3a**) in 37.4% yield. The ratio of the *cis*- and the *trans*-amines (*cis*- and *trans*-**3a**) in the crude product was estimated to be 7 to 1 from the <sup>1</sup>H-NMR spectrum. It is of interest that the diastereomerically pure *cis*-3,5-dimethoxy-acetamide (**13**) was obtained on catalytic reduction of the 3,5-dimethoxy-oxime (**4g**) over Raney nickel in acetic anhydride instead of ethanol as a solvent.

### 5. Hydrogenation of the Hydrazone (**15**) over Platinum Oxide

Hydrogenation of the trimethoxy-hydrazone (**15**) to the corresponding amine (**3a**) was also examined. Although common methods for preparation of hydrazones were not effective with the trimethoxy-tetralone (**1a**), treatment of the tetralone (**1a**) according to Barton's method<sup>16)</sup> gave the desired hydrazone (**15**) in good yield. Catalytic reduction of the hydrazone (**15**) over platinum oxide in acetic acid gave the pure *cis*-trimethoxy amine (*cis*-**3a**) in 76.7% yield.

### 6. Miscellaneous Methods

In 1958, Bixler *et al.*<sup>17)</sup> reported the reduction of oximes with stannous chloride and concentrated hydrochloric acid as a conventional method for preparation of amines from oximes. Therefore, the trimethoxy-oxime (**4a**) or -hydrazone (**15**) was treated with these reagents, but the result was recovery of the parent trimethoxy-tetralone (**1a**) in 99.4% or 74.7% yield. Treatment of the trimethoxy-hydrazone (**15**) with zinc powder in acetic acid also provided the parent tetralone (**1a**) in 56.8% yield.

In addition, we examined the hydrogenation of the hydrazone (**15**) over 10% palladium-carbon instead of platinum oxide. However, in this case, the stilbene (**5a**) was produced as the main product.<sup>18)</sup>

## 7. Conclusion

In the Robinson synthetic sequence for benzo[*c*]phenanthridine alkaloids, the step from the tetralone (**1**) to the formamide (**2**) is quite important. Leuckart reaction of the tetralones (**1**) seems to be suitable for this purpose, but gives essentially a complex mixture of the stilbene (**5**) and formamides (**2**) which are diastereomeric isomers of the desired formamide (**2**). Since the yield of the desired formamide (**2**) varied over a wide range as shown in Table I, these results indicate that the Leuckart reaction has limited applicability for the preparation of benzo[*c*]phenanthridine alkaloids.

The reduction of the oxime (**4**) under basic conditions, which gave a thermodynamically controlled product in the cases of other ring oximes, provided a diastereomeric mixture of the desired amines (**3**). This phenomenon could be ascribed to ring-flip of the 1-tetralone oxime ring system. In some cases, easy formation of the stilbene by  $\beta$ -elimination of a formamide molecule from the *cis*-formamide (*cis*-**2**) could decrease the yield in the step of formylation of the amine (**3**).

On the other hand, the reduction of the oxime (**4**) or the hydrazone (**15**) under acidic conditions tended to result in regeneration of the parent tetralone (**1**) or in formation of the stilbene (**5**) except in the case of catalytic hydrogenation.

Our experimental results led us to conclude that the step from the tetralone (**1**) to the formamide (**2**) in the Robinson synthetic sequence involves many problems which we were unable to solve, and that some improvements of this step are still required if it is to be suitable as a general method for the preparation of many alkaloids for structure-activity studies.

## Experimental

Instruments, etc., were as described in the preceding paper.<sup>1b)</sup>

**Leuckart Reaction of 6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (The Trimethoxy-tetralone) (1a)**—A mixture of the trimethoxy-tetralone<sup>1b)</sup> (**1a**) (5.09 g), HCONH<sub>2</sub> (70 ml), (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> (1.08 g), and HCOOH (3.2 ml) was heated at 160–170 °C for 9.5 h. The mixture was diluted with water and extracted with CHCl<sub>3</sub>. The chloroform solution was dried over K<sub>2</sub>CO<sub>3</sub> and evaporated to dryness *in vacuo*. The residue (6.13 g) was dissolved in benzene and chromatographed on Al<sub>2</sub>O<sub>3</sub>.

i) 6,7-Methylenedioxy-3-(3,4,5-trimethoxyphenyl)-1,2-dihydronaphthalene (The Trimethoxy-stilbene) (**5a**): In the column chromatography mentioned above, the eluate with benzene gave colorless needles (0.25 g), mp 120.5–121.5 °C, which were recrystallized from cyclohexane or MeOH. *Anal.* Calcd for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>: C, 70.57; H, 5.92. Found: C, 70.64; H, 5.84. IR  $\nu_{\max}$  cm<sup>-1</sup>: 1575 (C=C). <sup>1</sup>H-NMR  $\delta$ : 2.67 (4H, m, C<sub>1</sub>- and C<sub>2</sub>-H<sub>2</sub>), 3.71 (3H, s, OCH<sub>3</sub>), 3.81 (6H, s, OCH<sub>3</sub> × 2), 5.85 (2H, s, OCH<sub>2</sub>O), 6.52 and 6.57 (each 2H, s, arom. H<sup>19)</sup>), 6.55 (1H, s, arom. H<sup>19)</sup>). UV  $\lambda_{\max}$  nm (log  $\epsilon$ ): 225 (4.35), 338 (4.38).

ii) A Diastereomeric Mixture of *cis*- and *trans*-1-Formamido-6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalenes (The Trimethoxy-formamides) (**2a**): The subsequent eluate with CHCl<sub>3</sub> gave colorless cotton-like needles (3.93 g), mp 161–173 °C,<sup>7)</sup> which were recrystallized from EtOH. *Anal.* Calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>6</sub>: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.54; H, 6.02; N, 3.79. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3275 (NH), 1640 (CO).

***trans*-1-Formamido-6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (The *trans*-Trimethoxy-formamide) (*trans*-**2a**)**—Fractional recrystallization of the diastereomeric mixture (**2a**) (1.30 g) from CHCl<sub>3</sub>-benzene gave colorless pillars (0.63 g), mp 191.5–193.5 °C. *Anal.* Calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>6</sub>: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.54; H, 5.98; N, 3.51. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3250 (NH), 1665 and 1650 (CO). <sup>1</sup>H-NMR  $\delta$ : 1.86–2.25 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.60–3.00 (3H, m, C<sub>2</sub>-H and C<sub>4</sub>-H<sub>2</sub>), 3.83 (9H, s, OCH<sub>3</sub> × 3), 5.50<sup>20)</sup> (1H, q, *J* = 10.0 Hz, C<sub>1</sub>-H), 5.82 (1H, d, *J* = 10.0 Hz, NH), 5.91 (*ca.* 7/5H, s, OCH<sub>2</sub>O), 5.94 (*ca.* 3/5H, s, OCH<sub>2</sub>O), 6.41 (*ca.* 3/5H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.46 (*ca.* 7/5H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.55 (*ca.* 7/10H, s, arom. H), 6.70 (*ca.* 3/10H, s, arom. H), 6.77 (1H, s, arom. H), 8.15 (1H, s, NCHO); <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.80–2.20 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.67–3.00 (3H, m, C<sub>2</sub>-H and C<sub>4</sub>-H<sub>2</sub>), 3.62 (3H, s, OCH<sub>3</sub>), 3.73 (6H, s, OCH<sub>3</sub> × 2), 5.16 (1H, dif. t, *J* = 10.0 Hz, C<sub>1</sub>-H), 5.91 (2H, s, OCH<sub>2</sub>O), 6.54 (2H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.62<sup>21)</sup> (2H, dif. s, arom. H × 2), 8.00 (1H, s, NCHO), 8.21 (1H, dif. d, *J* = 10.0 Hz, NH).

**cis-1-Formamido-6,7-methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (The cis-Trimethoxy-formamide) (cis-2a)**—A part of the mixture (0.20 g) which was obtained from the mother liquor of the fractional recrystallization of the *trans*-trimethoxy-formamide (*trans*-2a) was purified by p-TLC on SiO<sub>2</sub> with benzene–AcOEt (3:7, v/v), followed by recrystallization from benzene to give colorless pillars (0.09 g), mp 178.5–180.5 °C. *Anal.* Calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>6</sub>: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.53; H, 6.04; N, 3.55. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3225 (NH), 1675 and 1650 (CO). <sup>1</sup>H-NMR  $\delta$ : 1.80–2.30 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.70–3.00 (2H, m, benzylic H  $\times$  2), 3.00–3.40 (1H, m, benzylic H), 3.81 (9H, s, OCH<sub>3</sub>  $\times$  3), 5.57<sup>22)</sup> (1H, dd,  $J$ =9.5 and 4.5 Hz, C<sub>1</sub>-H), 5.78 (1H, d,  $J$ =9.5 Hz, NH), 5.92 (ca. 4/3H, s, OCH<sub>2</sub>O), 5.95 (ca. 2/3H, s, OCH<sub>2</sub>O), 6.38 (ca. 2/3H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.42 (ca. 4/3H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.58, 6.63, and 6.82 (each ca. 2/3H, s, arom. H), 8.02 (1H, s, NCHO). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 1.70–2.20 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.64–3.20 (3H, m, C<sub>2</sub>-H and C<sub>4</sub>-H<sub>2</sub>), 3.62 (3H, s, OCH<sub>3</sub>), 3.73 (6H, s, OCH<sub>3</sub>  $\times$  2), 5.12–5.36 (1H, m, C<sub>1</sub>-H), 5.92 (2H, s, OCH<sub>2</sub>O), 6.50<sup>23)</sup> (ca. 2/5H, s, arom. H), 6.55<sup>23)</sup> (ca. 8/5H, s, arom. H), 6.65<sup>23)</sup> (ca. 3/2H, s, arom. H), 6.72<sup>23)</sup> (ca. 1/2H, s, arom. H), 7.78 (1H, s, NCHO), 8.18 (1H, d,  $J$ =10.0 Hz, NH).

**Treatment of the cis-Trimethoxy-formamide (cis-2a) with Formic Acid [The Trimethoxy-stilbene (5a)]**—A solution of the pure *cis*-trimethoxy-formamide (*cis*-2a) (0.10 g) in HCOOH (2 ml) was refluxed for 3 h. The mixture was diluted with a large amount of water and extracted with CHCl<sub>3</sub>. The chloroform solution was washed with 5% NaHCO<sub>3</sub> aq., dried over K<sub>2</sub>CO<sub>3</sub>, and evaporated to dryness. Purification of the residue by column chromatography on Al<sub>2</sub>O<sub>3</sub> (neutral, grade III) with benzene gave colorless needles (0.079 g), mp 120–121 °C, which were recrystallized from cyclohexane. This material was identical with the trimethoxy-stilbene (5a) described above.

**Treatment of the trans-Trimethoxy-formamide (trans-2a) with Formic Acid**—A solution of the pure *trans*-trimethoxy-formamide (*trans*-2a) (0.10 g) in HCOOH (0.35 ml) was refluxed for 3 h. The mixture was diluted with a large amount of water and extracted with CHCl<sub>3</sub>. The chloroform solution was washed with 5% NaHCO<sub>3</sub> aq., dried over K<sub>2</sub>CO<sub>3</sub>, and evaporated to dryness *in vacuo*. The residue was chromatographed on Al<sub>2</sub>O<sub>3</sub> with benzene followed by CHCl<sub>3</sub> and MeOH.

i) The Trimethoxy-stilbene (5a): The eluate with benzene gave colorless needles (0.023 g), mp 122–125 °C, which were recrystallized from benzene–MeOH. This material was identical with the trimethoxy-stilbene (5a) described above.

ii) The *trans*-Trimethoxy-formamide (*trans*-2a): The eluate with CHCl<sub>3</sub> and MeOH gave colorless needles (0.054 g), mp 191–194 °C, which were recrystallized from CHCl<sub>3</sub>–benzene. This material was identical with the *trans*-trimethoxy-formamide (*trans*-2a) described above.

**Treatment of a Diastereomeric Mixture of the Trimethoxy-formamides (2a) with Formic Acid**—A solution of the diastereomeric mixture of the trimethoxy-formamides (2a) (0.25 g) in HCOOH (3 ml) was refluxed for 3 h. After removal of a part of the solvent by distillation under reduced pressure, the mixture was diluted with a large quantity of water and extracted with CHCl<sub>3</sub>. The organic layer was washed with 5% Na<sub>2</sub>CO<sub>3</sub> aq., dried over K<sub>2</sub>CO<sub>3</sub>, and evaporated to dryness *in vacuo*. The residue was chromatographed on Al<sub>2</sub>O<sub>3</sub> (neutral, super grade) with CHCl<sub>3</sub>.

i) The Trimethoxy-stilbene (5a): The first eluate gave colorless needles (0.12 g), mp 120–121 °C, which were recrystallized from cyclohexane. This material was identical with the trimethoxy-stilbene (5a) described above.

ii) The *trans*-Trimethoxy-formamide (*trans*-2a): The second eluate gave colorless needles (0.090 g), mp 189–192 °C, which were recrystallized from CHCl<sub>3</sub>–benzene. This material was identical with the *trans*-trimethoxy-formamide (*trans*-2a) described above.

**trans-6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (The trans-Trimethoxy-amine) (trans-3a)**—A solution of the *trans*-trimethoxy-formamide (*trans*-2a) (0.47 g) in EtOH (30 ml) containing 6 N HCl aq. (10 ml) was refluxed for 6 h. The precipitate<sup>24)</sup> (0.45 g) was collected by filtration and dissolved in a small amount of MeOH. The methanolic solution was added to dil. NaOH aq. and extracted with Et<sub>2</sub>O. The ethereal solution was dried over K<sub>2</sub>CO<sub>3</sub> and evaporated. Recrystallization of the residue from MeOH gave colorless pillars (0.38 g), mp 125–126 °C. *Anal.* Calcd for C<sub>20</sub>H<sub>23</sub>NO<sub>5</sub>: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.23; H, 6.51; N, 3.99. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3360 and 3290 (NH). <sup>1</sup>H-NMR  $\delta$ : 1.67 (2H, s, NH<sub>2</sub>), 1.92–2.10 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.35–2.70 (1H, m, benzylic H), 2.70–2.90 (2H, m, benzylic H  $\times$  2), 3.87 (9H, s, OCH<sub>3</sub>  $\times$  3), 3.97 (1H, d,  $J$ =9.6 Hz, C<sub>1</sub>-H), 5.90 (2H, s, OCH<sub>2</sub>O), 6.48 (2H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.56 (1H, s, C<sub>5</sub>-H), 7.15 (1H, s, C<sub>8</sub>-H).

**cis-6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (The cis-Trimethoxy-amine) (cis-3a)**—A solution of the *cis*-trimethoxy-formamide (*cis*-2a) (0.31 g) in EtOH (30 ml) containing 6 N HCl aq. (9 ml) was refluxed for 6 h. The precipitate<sup>25)</sup> was collected by filtration and treated by the same procedure as described for the *trans*-trimethoxy-amine (*trans*-3a) to give colorless pillars (0.24 g), mp 144–147 °C, which were recrystallized from CHCl<sub>3</sub>–cyclohexane. The filtrate of the amine·HCl salt was basified with NaOH aq. and extracted with Et<sub>2</sub>O. The ethereal solution was dried over K<sub>2</sub>CO<sub>3</sub> and evaporated to give an additional amount of the material (0.029 g). *Anal.* Calcd for C<sub>20</sub>H<sub>23</sub>NO<sub>5</sub>: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.15; H, 6.57; N, 3.87. IR  $\nu_{\max}$  cm<sup>-1</sup>: 3350 and 3280 (NH). <sup>1</sup>H-NMR  $\delta$ : 1.40 (2H, s, NH<sub>2</sub>), 1.70–2.50 (2H, m, C<sub>3</sub>-H<sub>2</sub>), 2.70–3.17 (3H, m, C<sub>2</sub>-H and C<sub>4</sub>-H<sub>2</sub>), 3.87 (9H, s, OCH<sub>3</sub>  $\times$  3), 4.02 (1H, d,  $J$ =3.4 Hz, C<sub>1</sub>-H), 5.90 (2H, s, OCH<sub>2</sub>O), 6.48 (2H, s, C<sub>2</sub>- and C<sub>6</sub>-H), 6.58 (1H, s, C<sub>5</sub>-H), 6.75 (1H, s, C<sub>8</sub>-H).

**Formylation of the trans-Trimethoxy-amine (trans-3a) [The trans-Trimethoxy-formamide (trans-2a)]**—A mixture of the *trans*-trimethoxy-amine (*trans*-3a) (0.10 g) and HCONH<sub>2</sub> (3 ml) was heated at 150 °C for 2 h. The mixture

was diluted with water and extracted with  $\text{CHCl}_3$ . The chloroform solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. Recrystallization of the residue from  $\text{CHCl}_3$ -benzene gave colorless pillars (0.043 g), mp 189—191 °C. This material was identical with the *trans*-trimethoxy-formamide (*trans*-2a) described above.

**Formylation of the *cis*-Trimethoxy-amine (*cis*-3a) [The *cis*-Trimethoxy-formamide (*cis*-2a)]**—A mixture of the *cis*-trimethoxy-amine (*cis*-3a) (0.19 g) and  $\text{HCONH}_2$  (3.5 ml) was heated at 150 °C for 1 h. The mixture was diluted with water and extracted with  $\text{CHCl}_3$ . The chloroform solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene gave colorless needles (0.084 g), mp 180—181 °C, which were identical with the *cis*-trimethoxy-formamide (*cis*-2a) described above.

**Leuckart Reaction of 2-(3-Methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (The Monomethoxy-tetralone) (1c) [The Monomethoxy-formamide (2c)]**—According to the reported method,<sup>5)</sup> monomethoxy-tetralone (1c), mp 94—96 °C (lit.<sup>5)</sup> mp 95—96 °C), was prepared from commercial 1-tetralone and *o*-chloroanisole in 36.5% yield. A mixture of the monomethoxy-tetralone (1c) (1.00 g),  $(\text{NH}_4)_2\text{SO}_4$  (0.43 g),  $\text{HCOOH}$  (0.8 ml), and  $\text{HCONH}_2$  (20 ml) was refluxed for 4 h. The mixture was diluted with a large amount of water and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with 5%  $\text{Na}_2\text{CO}_3$  aq. and dried over  $\text{K}_2\text{CO}_3$ . Purification of the residue by column chromatography on  $\text{SiO}_2$  with  $\text{CHCl}_3$  gave colorless plates (0.65 g), mp 144.5—147.5 °C, which were recrystallized from  $\text{CHCl}_3$ -benzene. This material was essentially identical with the monomethoxy-formamide (2c) described below.

**Leuckart Reaction of 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2H)-one (The 2-Methoxy-4,5-methylenedioxy-tetralone) (1d)**—A mixture of the 2-methoxy-4,5-methylenedioxy-tetralone<sup>1b)</sup> (1d) (0.20 g),  $\text{HCONH}_2$  (3 ml),  $\text{HCOOH}$  (0.2 ml), and  $(\text{NH}_4)_2\text{SO}_4$  (0.048 g) was heated at 170 °C for 6 h. The mixture was diluted with water and extracted with  $\text{CHCl}_3$ . The chloroform solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. The residue was chromatographed on  $\text{SiO}_2$  with benzene.

i) 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxynaphthalene (The 2-Methoxy-4,5-methylenedioxy-naphthalene) (6d): The eluate with benzene gave colorless needles (0.017 g), mp 208—210 °C, which were recrystallized from benzene-hexane. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{14}\text{O}_5$ : C, 70.80; H, 4.38. Found: C, 70.76; H, 4.35. UV  $\lambda_{\text{max}}$  nm (log  $\epsilon$ ): 231 (4.39), 254 (4.18), 317 (3.89). MS  $m/z$ : 322 ( $\text{M}^+$ , 100%).

This material was considered to have been formed by air-oxidation of the stilbene product (5d).

ii) 1-Formamido-2-(2-methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (The 2-Methoxy-4,5-methylenedioxy-formamide) (2d): The eluate with  $\text{CHCl}_3$  gave an oily product (0.048 g), which gradually crystallized over a long period. This material was essentially identical with the 2-methoxy-4,5-methylenedioxy-formamide (2d) described below. IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3430 (NH) br, 1680 (CO).  $^1\text{H-NMR}$   $\delta$ : 1.75—2.20 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.70—3.00 (2H, m, benzylic H  $\times$  2), 3.10—3.60 (1H, m, benzylic H), 3.75 (6/3H, s, *trans*- $\text{OCH}_3$ ), 3.81 (3/3H, s, *cis*- $\text{OCH}_3$ ), 5.24<sup>26)</sup> (2/3H, t,  $J = 10.0$  Hz, *trans*- $\text{C}_1\text{-H}$ ), 5.58 (1/3H, dif. d,  $J = 4.5$  Hz, *cis*- $\text{C}_1\text{-H}$ ), 5.88 (5H, dif. s,  $\text{OCH}_2\text{O} \times 2$  and NH), 6.50—6.80 (4H, m, arom. H  $\times$  4), 7.85 (1/3H, s, *cis*-NCHO), 8.09 (2/3H, s, *trans*-NCHO).

**Leuckart Reaction of 2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2H)-one (The 5-Methoxy-2,3-methylenedioxy-tetralone) (1e) [The 5-Methoxy-2,3-methylenedioxy-formamide (2e)]**—A mixture of the 5-methoxy-2,3-methylenedioxy-tetralone<sup>1b)</sup> (1e) (0.20 g),  $\text{HCONH}_2$  (0.5 ml),  $(\text{NH}_4)_2\text{SO}_4$  (0.027 g), and  $\text{HCOOH}$  (0.027 ml) was heated at 180 °C. Additional  $\text{HCOOH}$  (0.027 ml) was added to the mixture every 1 h. Addition of  $\text{HCOOH}$  was halted after 4 h, but the mixture was further heated at 145 °C for 4 h. When the reaction was completed, the mixture was diluted with a large amount of water and extracted with  $\text{CHCl}_3$ . The chloroform solution was dried over  $\text{MgSO}_4$  and evaporated to dryness *in vacuo*. The residue was chromatographed on  $\text{SiO}_2$  with benzene. After elution with benzene and with 5%  $\text{AcOEt}$  in benzene, the eluate with 10%  $\text{AcOEt}$  in benzene gave colorless needles (0.075 g), mp 166—182 °C, which were recrystallized from benzene. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3305 and 3225 (NH), 1678 and 1650 (CO); IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3420 (NH), 1690 (CO). This material was essentially identical with the 5-methoxy-2,3-methylenedioxy-formamide (2e) described below.

**Leuckart Reaction of 6,7-Methylenedioxy-2-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (The Avicine-tetralone) (1f)**—A mixture of the avicine-tetralone<sup>1b,4b)</sup> (1f) (5.00 g),  $(\text{NH}_4)_2\text{SO}_4$  (1.09 g),  $\text{HCOOH}$  (2.75 ml), and  $\text{HCONH}_2$  (65 ml) was heated at 160—165 °C for 6 h under argon. The reaction mixture was poured into water and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with sat.  $\text{NaCl}$  aq., dried over  $\text{MgSO}_4$ , and evaporated to dryness. The residue was chromatographed on  $\text{Al}_2\text{O}_3$  with abs. benzene followed by  $\text{CHCl}_3$ .

i) 6,7-Methylenedioxy-3-(3,4-methylenedioxyphenyl)-1,2-dihydronaphthalene (The Avicine-stilbene) (5f): The eluate with abs. benzene gave colorless needles (0.32 g), mp 152—160 °C (lit.<sup>4b)</sup> mp 155 °C), which were recrystallized from benzene-hexane.

ii) 1-Formamido-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene (The Avicine-formamide) (2f): The eluate with  $\text{CHCl}_3$  gave colorless needles (3.23 g), mp 168—174 °C (lit.<sup>4b)</sup> mp 169—170 °C), which were recrystallized from  $\text{EtOH}$ . IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3250 (NH), 1650 (CO).  $^1\text{H-NMR}$   $\delta$ : 1.92—2.16 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.65—2.92 (3H, m,  $\text{C}_2\text{-H}$  and  $\text{C}_4\text{-H}_2$ ), 5.15—5.52<sup>27)</sup> (1H, m,  $\text{C}_1\text{-H}$ ), 5.72 (1H, br s, NH), 5.86 and 5.90 (each 2H, s,  $\text{OCH}_2\text{O}$ ), 6.35 (1H, m, arom. H), 6.64—6.78 (4H, m, arom. H  $\times$  4), 7.94 (ca. 1/3H, s, *cis*-NCHO), 8.08 (ca. 2/3H, s, *trans*-NCHO).

**6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one Oxime (The Trimethoxy-oxime)**

**(4a)**—A solution of the trimethoxy-tetralone<sup>1b</sup> (**1a**) (0.23 g) and  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (0.21 g) in dry pyridine (3 ml) was refluxed for 3.5 h. The reaction mixture was diluted with water and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with sat.  $\text{CuSO}_4$  aq., dried over  $\text{MgSO}_4$ , and evaporated to dryness *in vacuo*. Recrystallization of the residue from  $\text{EtOH}-\text{CHCl}_3$  or  $\text{CHCl}_3$ -benzene gave colorless prisms (0.20 g), mp 232–234 °C. *Anal.* Calcd for  $\text{C}_{20}\text{H}_{21}\text{NO}_6$ : C, 64.68; H, 5.70; N, 3.77. Found: C, 64.58; H, 5.70; N, 3.66. IR  $\nu_{\text{max}} \text{ cm}^{-1}$ : 3330 (OH).  $^1\text{H-NMR}$   $\delta$ : 2.08 (2H,  $\text{C}_3\text{-H}_2$ ), 2.52 (2H, m,  $\text{C}_4\text{-H}_2$ ), 3.73 (6H, s,  $\text{OCH}_3 \times 2$ ), 3.77 (3H, s,  $\text{OCH}_3$ ), 4.67 (1H, m,  $\text{C}_2\text{-H}$ ), 5.92 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.35 (2H, s,  $\text{C}_2\text{-}$  and  $\text{C}_6\text{-H}$ ), 6.54 (1H, s,  $\text{C}_5\text{-H}$ ), 7.45 (1H, s,  $\text{C}_8\text{-H}$ ), 8.20 (1H, br s, OH).

**Reduction of the Trimethoxy-oxime (4a) with Sodium Metal in Ethanol [The Undefined Dimethoxy-amine (3g)]**—Sodium metal (2.70 g) was added portionwise to a stirred solution of the trimethoxy-oxime (**4a**) (0.40 g) in abs.  $\text{EtOH}$  (4 ml) under reflux. When the starting oxime (**4a**) had been consumed, as checked by TLC (*ca.* 4 h), the mixture was acidified with conc.  $\text{HCl}$  and extracted with  $\text{Et}_2\text{O}$ . The aqueous layer was basified with 10%  $\text{NaOH}$  aq. and extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and then evaporated. Purification of the residue by column chromatography on  $\text{Al}_2\text{O}_3$  (basic, grade I) with benzene gave an oil (0.24 g).  $^1\text{H-NMR}$   $\delta$ : 2.08 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.31 (2H, m,  $\text{NH}_2$ ), 2.82 (3H, m,  $\text{C}_2\text{-H}$  and  $\text{C}_4\text{-H}_2$ ), 3.79 (6H, s,  $\text{OCH}_3 \times 2$ ), 4.01 (1H, d,  $J=3.5 \text{ Hz}$ ,  $\text{C}_1\text{-H}$ ), 5.88 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.34–6.59 (5H, m, arom.  $\text{H} \times 5$ ).

This oily material was characterized as the hydrochloride salt, which was prepared by the usual method. Recrystallization of the salt from  $\text{Et}_2\text{O}-\text{EtOH}$  gave colorless needles, mp 223–226 °C. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl}$ : C, 62.72; H, 6.10; N, 3.85. Found: C, 62.55; H, 6.47; N, 3.77.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 1.90–2.20 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.10–3.05 (3H, m,  $\text{C}_2\text{-H}$  and  $\text{C}_4\text{-H}_2$ ), 3.75<sup>28</sup>) and 3.81<sup>28</sup>) (each 3H, s,  $\text{OCH}_3$ ), 4.50–4.65 (1H, m,  $\text{C}_1\text{-H}$ ), 5.95 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.40–7.07<sup>29</sup>) (5H, m, arom.  $\text{H} \times 5$ ).

**Acetylation of the Undefined Dimethoxy-amine (3g) [The Undefined Dimethoxy-acetamide (13)]**—The above crude amine (**3g**) (0.47 g) was dissolved in pyridine (5 ml) and stirred with  $\text{Ac}_2\text{O}$  (5 ml) at room temperature for 3 h. The mixture was poured into water, made acidic with 10%  $\text{HCl}$  aq., and extracted with  $\text{CHCl}_3$ . The chloroform solution was dried over  $\text{MgSO}_4$  and evaporated to dryness. p-TLC of the residue (0.37 g) on  $\text{SiO}_2$  with benzene– $\text{AcOEt}$  (2:1, v/v) gave a crystal mass (0.14 g), mp 210–220 °C.  $^1\text{H-NMR}$   $\delta$ : 1.76 and 1.85 (total 3H, each s,  $\text{COCH}_3$ ), 1.88–2.20 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.79 (2H, t,  $J=6.0 \text{ Hz}$ ,  $\text{C}_4\text{-H}_2$ ), 3.05–3.35 (1H, m,  $\text{C}_2\text{-H}$ ), 3.75 (6H, s,  $\text{OCH}_3 \times 2$ ), 5.20–5.70<sup>30</sup>) (2H, m,  $\text{C}_1\text{-H}$  and  $\text{NH}$ ), 5.87 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.32 (3H, s,  $\text{C}_2\text{-}$ ,  $\text{C}_4\text{-}$ , and  $\text{C}_6\text{-H}$ ), 6.52 and 6.55 (total 1H, each s,  $\text{C}_5\text{-H}$ ), 6.73 (*ca.* 1/5H, s, *trans*- $\text{C}_8\text{-H}$ ), 6.78 (*ca.* 4/5H, s, *cis*- $\text{C}_8\text{-H}$ ). This material was so labile that it was used for the subsequent elimination reaction without purification.

**Treatment of the Undefined Dimethoxy-acetamide (13) with Formic Acid [The Undefined Dimethoxy-stilbene (5g)]**—A solution of the crude acetamide (**13**) (0.26 g) in  $\text{HCOOH}$  (13 ml) was refluxed for 1.5 h. The mixture was diluted with water and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with 10%  $\text{NaHCO}_3$  aq., dried over  $\text{K}_2\text{CO}_3$ , and evaporated to dryness *in vacuo*. Purification of the residue by column chromatography on  $\text{SiO}_2$  with benzene gave colorless prisms (0.13 g), mp 130–133 °C. This material was so labile that it was used for the next step without further purification.

**Dehydrogenation of the Undefined Dimethoxy-stilbene (5g) [The Undefined Dimethoxy-naphthalene (6g)]**—A solution of the undefined stilbene (**5g**) (0.12 g) in *p*-cymene (3.3 ml) in the presence of 30%  $\text{Pd-C}$  (0.06 g) was refluxed for 2.5 h under argon. After removal of the catalyst by filtration, the filtrate was diluted with hexane and chromatographed on  $\text{Al}_2\text{O}_3$  with hexane. After elution with hexane (*p*-cymene-containing fraction), the eluate with  $\text{CHCl}_3$  provided colorless prisms (0.068 g), mp 174–175.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{16}\text{O}_4$ : C, 74.01; H, 5.23. Found: C, 74.07; H, 5.15. IR  $\nu_{\text{max}} \text{ cm}^{-1}$ : 1590 ( $\text{C}=\text{C}$ ). This material was identical with a sample of 2-(3,5-dimethoxyphenyl)-6,7-methylenedioxy-naphthalene (**6g**) prepared from the 3,5-dimethoxy-tetralone (**1g**).

**2-(3,5-Dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2H)-one Oxime (The 3,5-Dimethoxy-oxime) (4g)**—A solution of the 3,5-dimethoxy-tetralone<sup>1b</sup> (**1g**) (0.10 g) and  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (0.11 g) in dry pyridine (1 ml) was heated at 100 °C for 3 h. The mixture was poured into water and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with sat.  $\text{CuSO}_4$  aq., dried over  $\text{MgSO}_4$ , and evaporated to dryness *in vacuo*. Recrystallization of the residue from  $\text{CHCl}_3$ -hexane gave colorless needles (0.039 g), mp 204–206 °C. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_5$ : C, 66.85; H, 5.61; N, 4.10. Found: C, 66.34; H, 5.60; N, 4.00. IR  $\nu_{\text{max}} \text{ cm}^{-1}$ : 3225 (OH).  $^1\text{H-NMR}$ <sup>31</sup>) ( $\text{DMSO}-d_6$ )  $\delta$ : 2.00 (2H, m,  $\text{C}_3\text{-H}_2$ ), 3.68 (6H, s,  $\text{OCH}_3 \times 2$ ), 4.54 (1H, t,  $J=3.8 \text{ Hz}$ ,  $\text{C}_2\text{-H}$ ), 5.96 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.15–6.32 (3H, m,  $\text{C}_2\text{-}$ ,  $\text{C}_4\text{-}$ , and  $\text{C}_6\text{-H}$ ), 6.63 (1H, s,  $\text{C}_5\text{-H}$ ), 7.38 (1H, s,  $\text{C}_8\text{-H}$ ), 10.82 (1H, s, OH).

**Reduction of the 3,5-Dimethoxy-oxime (4g) with Sodium Amalgam [2-(3,5-Dimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-naphthylamine (The 3,5-Dimethoxy-amine) (3g)]**—Sodium amalgam (5%) (16.0 g) was added portionwise to a suspension of the 3,5-dimethoxy-oxime (**4g**) (0.10 g) in abs.  $\text{EtOH}$  (16.0 ml) at 60 °C. During the reaction, the mixture was adjusted to be slightly acidic by addition of 50%  $\text{AcOH}-\text{EtOH}$ . After the reaction was complete, the Hg metal formed was removed by decantation. The reaction mixture was evaporated under reduced pressure. After addition of water, the residue was acidified with conc.  $\text{HCl}$  and extracted with  $\text{CHCl}_3$ . The chloroform solution was extracted with 10%  $\text{HCl}$  aq. The aqueous layers were combined, basified with 15%  $\text{KOH}$  aq., and extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with water, dried over  $\text{K}_2\text{CO}_3$ , and evaporated to dryness. Purification of the residue by p-TLC on  $\text{SiO}_2$  with benzene– $\text{AcOEt}$  (2:1, v/v) gave an oil (0.034 g). MS

$m/z$ : 327 ( $M^+$ , 3.9%), 164 (100%).

This material was acetylated without further purification.

**Acetylation of the 3,5-Dimethoxy-amine (3g) [1-Acetamido-2-(3,5-dimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (13)]**—The oily 3,5-dimethoxy-amine (3g) (0.10 g) described above was dissolved in pyridine (1 ml) and stirred with  $Ac_2O$  (1 ml) at room temperature for 3 h. The mixture was acidified with 10% HCl aq. and extracted with  $Et_2O$ . The ethereal solution was washed with 5%  $NaHCO_3$  aq., dried over  $K_2CO_3$ , and evaporated. Recrystallization of the residue from  $CHCl_3$ –hexane gave colorless needles (0.071 g), mp 222–224 °C. *Anal.* Calcd for  $C_{21}H_{23}NO_5$ : C, 68.28; H, 6.28; N, 3.79. Found: C, 67.70; H, 6.23; N, 3.64. IR  $\nu_{max}$   $cm^{-1}$ : 3240 (NH), 1640 (CO).  $^1H$ -NMR  $\delta$ : 1.74 (ca. 9/5H, s, *cis*- $COCH_3$ ), 1.83 (ca. 6/5H, s, *trans*- $COCH_3$ ), 1.90–2.25 (2H, m,  $C_3$ - $H_2$ ), 2.75 (2H, t,  $J$  = 6.5 Hz,  $C_4$ - $H_2$ ), 3.00–3.35 (1H, m,  $C_2$ -H), 3.73 (6H, s,  $OCH_3 \times 2$ ), 5.20–5.70<sup>(32)</sup> (2H, m,  $C_1$ -H and NH), 5.86 (2H, s,  $OCH_2O$ ), 6.30 (3H, dif. s,  $C_2$ -,  $C_4$ -, and  $C_6$ -H), 6.50 and 6.53 (total 1H, each s,  $C_5$ -H), 6.73 (ca. 2/5H, s, *trans*- $C_8$ -H), 6.78 (ca. 3/5H, s, *cis*- $C_8$ -H).

**Hydrogenation of the 3,5-Dimethoxy-oxime (4g) in Acetic Anhydride over Raney Nickel [cis-1-Acetamido-2-(3,5-dimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (*cis*-13)]**—The 3,5-dimethoxy-oxime (4g) (0.10 g) in  $Ac_2O$  (5 ml) was hydrogenated in the presence of Raney Ni (ca. 0.05 g) at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. Purification of the residue by p-TLC on  $SiO_2$  with benzene– $AcOEt$  (2:1, v/v) gave colorless needles (0.045 g), mp 233–235 °C, which were recrystallized from  $CHCl_3$ –hexane. *Anal.* Calcd for  $C_{21}H_{23}NO_5$ : C, 68.28; H, 6.28; N, 3.79. Found: C, 67.96; H, 6.36; N, 3.80. IR  $\nu_{max}$   $cm^{-1}$ : 3240 (NH), 1640 (CO). UV  $\lambda_{max}$  nm (log  $\epsilon$ ): 282 (3.69), 294 (3.66).  $^1H$ -NMR  $\delta$ : 1.76 (3H, s,  $COCH_3$ ), 1.90–2.25 (2H, m,  $C_3$ - $H_2$ ), 2.79 (2H, t,  $J$  = 6.5 Hz,  $C_4$ - $H_2$ ), 3.05–3.35 (1H, m,  $C_2$ -H), 3.75 (6H, s,  $OCH_3 \times 2$ ), 5.30–5.80<sup>(33)</sup> (2H, m,  $C_1$ -H and NH), 5.88 (2H, s,  $OCH_2O$ ), 6.33 (3H, s,  $C_2$ -,  $C_4$ -, and  $C_6$ -H), 6.56 (1H, s,  $C_5$ -H), 6.80 (1H, s,  $C_8$ -H).

**3-(3,5-Dimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene (The 3,5-Dimethoxy-stilbene) (5g)**—A solution of the *cis*-dimethoxy-acetamide (*cis*-13) (0.15 g) in  $HCOOH$  (7.5 ml) was refluxed for 3 h. The mixture was diluted with a large amount of water and extracted with  $CHCl_3$ . The chloroform solution was washed with 5%  $NaHCO_3$  aq., dried over  $K_2CO_3$ , and evaporated to dryness *in vacuo*. Column chromatography of the residue on  $SiO_2$  with benzene gave a crystal mass (0.095 g), mp 125–130 °C. This material was so labile that the crude product was used in the subsequent experiment without further purification. IR  $\nu_{max}$   $cm^{-1}$ : 1605 (C=C). MS  $m/z$ : 310 ( $M^+$ , 100%).

**6-(3,5-Dimethoxyphenyl)-2,3-methylenedioxynaphthalene (The 3,5-Dimethoxy-naphthalene) (6g)**—A solution of the crude 3,5-dimethoxy-stilbene (5g) (0.070 g) in *p*-cymene (1.65 ml) containing 30% Pd-C (0.030 g) was refluxed for 2 h under argon. After removal of the catalyst by filtration, the filtrate was dissolved in hexane and chromatographed on  $Al_2O_3$ . After elution with hexane (*p*-cymene-containing fraction), the eluate with  $CHCl_3$  gave a crude material. Purification of the residue by p-TLC on  $SiO_2$  with  $Et_2O$ –cyclohexane (8:5, v/v) followed by recrystallization from benzene–hexane gave colorless prisms (0.025 g), mp 170–172.5 °C. *Anal.* Calcd for  $C_{19}H_{16}O_4$ : C, 74.01; H, 5.23. Found: C, 74.15; H, 5.40. IR  $\nu_{max}$   $cm^{-1}$ : 1590 (C=C). UV  $\lambda_{max}$  nm (log  $\epsilon$ ): 226 (4.57), 254 (4.67), 286 (4.18), 335 (3.61).  $^1H$ -NMR  $\delta$ : 3.82 (6H, s,  $OCH_3 \times 2$ ), 5.97 (2H, s,  $OCH_2O$ ), 6.44 (1H, t,  $J$  = 2.5 Hz,  $C_4$ -H), 6.79 (2H, d,  $J$  = 2.5 Hz,  $C_2$ - and  $C_6$ -H), 7.08 and 7.12 (each 1H, s,  $C_5$ - and  $C_8$ -H), 7.52 (1H, dd,  $J$  = 8.0 and 2.0 Hz,  $C_3$ -H), 7.68 (1H, d,  $J$  = 8.0 Hz,  $C_4$ -H), 7.81 (1H, br s,  $C_1$ -H). MS  $m/z$ : 308 ( $M^+$ , 100%).

**Reduction of the Monomethoxy-oxime (4c) with Sodium Metal in Ethanol [2-(3-Methoxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (The Monomethoxy-amine) (3c)]**—According to the reported method,<sup>5)</sup> the monomethoxy-oxime (4c), mp 125–128 °C (lit.<sup>5)</sup> mp 130–131.5 °C), was prepared from the monomethoxy-tetralone (1c) in 82.2% yield. Sodium metal (1.29 g) was added portionwise to a solution of the oxime (4c) (0.20 g) in abs. EtOH (3.1 ml). The reaction mixture was refluxed for 1 h, then the mixture was poured into water, acidified with conc. HCl, and extracted with  $Et_2O$ . The aqueous solution was basified with 10% NaOH aq. and extracted with  $Et_2O$ . The ethereal solution was dried over  $K_2CO_3$  and evaporated to dryness *in vacuo* to give a pale yellow oil (0.14 g).  $^1H$ -NMR  $\delta$ : 1.43 (2H, br s,  $NH_2$ ), 1.80–2.20 (2H, m,  $C_3$ - $H_2$ ), 2.85–3.25 (3H, m,  $C_2$ -H and  $C_4$ - $H_2$ ), 3.80 (3H, s,  $OCH_3$ ), 4.03 (ca. 1/3H, br s,  $C_1$ -H), 4.12 (ca. 2/3H, d,  $J$  = 3.0 Hz,  $C_1$ -H), 6.70–6.94 (3H, m, arom. H  $\times$  3), 7.00–7.38 (5H, m, arom. H  $\times$  5).

This material could be crystallized as the hydrochloride, colorless needles, mp 209–212 °C, *N*-acetate, colorless needles, mp 147.5–151 °C (lit.<sup>5)</sup> mp 149–151 °C), or *N*-benzoate, colorless needles, mp 176–179 °C (lit.<sup>5)</sup> mp 181–182 °C) according to the reported method.<sup>5)</sup>

**Formylation of the Monomethoxy-amine (3c) [1-Formamido-2-(3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (2c)]**—A solution of the amine (3c) (0.32 g) in  $HCONH_2$  (10 ml) was heated at 170 °C for 5 h. The mixture was diluted with water and extracted with  $CHCl_3$ . The chloroform solution was dried over  $K_2CO_3$  and evaporated to dryness *in vacuo*. Recrystallization of the residue from  $CHCl_3$ –benzene gave colorless needles (0.25 g), mp 144–147 °C. *Anal.* Calcd for  $C_{18}H_{19}NO_2$ : C, 76.84; H, 6.81; N, 4.98. Found: C, 76.76; H, 6.82; N, 4.94. IR  $\nu_{max}$   $cm^{-1}$ : 3290 (NH), 1650 (CO).  $^1H$ -NMR  $\delta$ : 1.80–2.30 (2H, m,  $C_3$ - $H_2$ ), 2.70–3.05 (3H, m,  $C_2$ -H and  $C_4$ - $H_2$ ), 3.73 (ca. 6/5H, s,  $OCH_3$ ), 3.77 (ca. 9/5H, s,  $OCH_3$ ), 5.45–5.98<sup>(34)</sup> (2H, m,  $C_1$ -H and NH), 6.60–6.85 (3H, m, arom. H  $\times$  3), 7.00–7.37 (5H, m, arom. H  $\times$  5), 7.88 (ca. 3/5H, s, NCHO), 8.04 (ca. 2/5H, s, NCHO).

**2-(2-Methoxy-4,5-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2H)-one Oxime (The 2-Methoxy-4,5-methylenedioxy-oxime) (4d)**—A solution of the 2-methoxy-4,5-methylenedioxy-tetralone<sup>1b)</sup> (1d) (1.15 g) and  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (1.15 g) in dry pyridine (10 ml) was heated at 100 °C for 3 h. The mixture was poured into a large amount of water and extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was washed with 5%  $\text{HCl}$  aq., dried over  $\text{MgSO}_4$ , and evaporated to dryness *in vacuo*. Recrystallization of the residue from  $\text{CHCl}_3$ - $\text{EtOH}$  gave colorless needles (0.98 g), mp 242–243 °C. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{17}\text{NO}_6$ : C, 64.22; H, 4.82; N, 3.94. Found: C, 63.86; H, 4.85; N, 4.12. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3200 (OH).  $^1\text{H-NMR}$  (pyridine- $d_5$ )  $\delta$ : 2.00–2.30 (2H, m,  $\text{C}_3$ - $\text{H}_2$ ), 2.50–2.80 (2H, m,  $\text{C}_4$ - $\text{H}_2$ ), 3.76 (3H, s,  $\text{OCH}_3$ ), 5.48 (1H, t,  $J=4.0$  Hz,  $\text{C}_2$ -H), 5.80 and 5.86 (each 1H, s,  $\text{OCH}_2\text{O}$ ), 5.96 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.65, 6.76, 6.79, and 8.00 (each 1H, s, arom. H), 12.98 (1H, s, OH).

**Reduction of the 2-Methoxy-4,5-methylenedioxy-oxime (4d) with Sodium Metal in Ethanol**—Sodium metal (3.4 g) was added portionwise to a stirred suspension of the 2-methoxy-4,5-methylenedioxy-oxime (4d) (1.20 g) in abs.  $\text{EtOH}$  (30 ml). After the addition, the reaction mixture was refluxed for 7 h, made acidic with conc.  $\text{HCl}$ , and evaporated to dryness *in vacuo*. The residue was dissolved in water and extracted with  $\text{Et}_2\text{O}$ . The aqueous solution was made alkaline with 10%  $\text{NaOH}$  aq. and extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on  $\text{Al}_2\text{O}_3$  (basic, grade I).

i) **2-(2-Methoxy-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-1-naphthylamine (The 2-Methoxy-4,5-methylenedioxy-amine) (3d)**: The eluate with  $\text{CHCl}_3$  was transformed into the hydrochloride, colorless needles (0.25 g), mp 254–260 °C, which were recrystallized from  $\text{EtOH}$ - $\text{Et}_2\text{O}$ . The hydrochloride was converted into the free amine in the usual manner to give colorless needles, mp 159–162 °C, which were recrystallized from  $\text{MeOH}$ . This material was essentially identical with a diastereomeric mixture of the 2-methoxy-4,5-methylenedioxy-amine (3d) described below.

ii) **The Undefined Amine (14)**: The eluate with  $\text{EtOH}$  gave colorless prisms (14) (0.060 g), mp 245–247 °C, which were recrystallized from dioxane- $\text{EtOH}$ . IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3340 and 3270 (NH).  $^1\text{H-NMR}$  (pyridine- $d_5$ )  $\delta$ : 3.60 and 3.66 (each 3H, s,  $\text{OCH}_3$ ), 5.94 (2H, s,  $\text{OCH}_2\text{O}$ ). MS  $m/z$ : 327 ( $\text{M}^+$ , 3.3%), 135 (100%).

**Reduction of the Trimethoxy-oxime (4a) with Sodium Amalgam [The Trimethoxy-amine (3a)]**—Sodium amalgam (5%) (52 g) was added portionwise to a solution of the trimethoxy-oxime (4a) (0.30 g) in abs.  $\text{EtOH}$  (40 ml) at 50–60 °C. During the reaction, the mixture was adjusted to be slightly acidic by addition of  $\text{AcOH}$ . After completion of the reaction (monitored by TLC), the Hg metal formed was removed by decantation. The reaction mixture was concentrated by distillation under reduced pressure, acidified with 5%  $\text{HCl}$  aq., and extracted with  $\text{Et}_2\text{O}$ . The aqueous solution was basified with 10%  $\text{NaOH}$  aq. and extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness. Recrystallization of the residue from  $\text{EtOH}$  gave colorless pillars (0.13 g), mp 143–148 °C. *Anal.* Calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_5$ : C, 67.21; H, 6.49; N, 3.92. Found: C, 67.25; H, 6.49; N, 3.88. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3350 and 3270 (NH).  $^1\text{H-NMR}$   $\delta$ : 1.66 (2H, br s,  $\text{NH}_2$ ), 1.80–2.50 (2H, m,  $\text{C}_3$ - $\text{H}_2$ ), 2.70–3.16 (3H, m,  $\text{C}_2$ -H and  $\text{C}_4$ - $\text{H}_2$ ), 3.77 (9H, s,  $\text{OCH}_3 \times 3$ ), 3.94 (ca. 3/7H, d,  $J=ca.$  9.6 Hz, *trans*- $\text{C}_1$ -H), 4.01 (ca. 4/7H, d,  $J=3.0$  Hz, *cis*- $\text{C}_1$ -H), 5.89 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.45 (ca. 6/7H, s, *trans*- $\text{C}_2$ - and *trans*- $\text{C}_6$ -H), 6.47 (ca. 8/7H, s, *cis*- $\text{C}_2$ - and *cis*- $\text{C}_6$ -H), 6.54 (ca. 3/7H, s, *trans*- $\text{C}_5$ -H), 6.57 (ca. 4/7H, s, *cis*- $\text{C}_5$ -H), 6.75 (ca. 4/7H, s, *cis*- $\text{C}_8$ -H), 7.13 (ca. 3/7H, s, *trans*- $\text{C}_8$ -H).

**Reduction of the Monomethoxy-oxime (4c) with Sodium Amalgam [The Monomethoxy-amine (3c)]**—Sodium amalgam (5%) (18.0 g) was added portionwise to a solution of the oxime (4c) (0.20 g) in abs.  $\text{EtOH}$  (17.5 ml) at 50 °C. During the addition, the mixture was kept neutral or a slightly acidic with  $\text{AcOH}$ . After addition of  $\text{Na-Hg}$ , the mixture was refluxed for 3 h. The Hg metal formed was removed by decantation and a part of the solvent was distilled off under reduced pressure. The mixture was acidified with 5%  $\text{HCl}$  aq. and extracted with  $\text{Et}_2\text{O}$ . The aqueous solution was basified with 5%  $\text{NaOH}$  aq. and extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. This material, a slightly yellow oil (0.15 g), was essentially identical with the monomethoxy-amine (3c) described above.

**Reduction of the 2-Methoxy-4,5-methylenedioxy-oxime (4d) with Sodium Amalgam [The 2-Methoxy-4,5-methylenedioxy-amine (3d)]**—Sodium amalgam (5%) (230 g) was added portionwise to a suspension of the 2-methoxy-4,5-methylenedioxy-oxime (4d) (1.52 g) in abs.  $\text{EtOH}$  (230 ml) at 60 °C. During the reaction, the reaction mixture was kept slightly acidic by addition of 50%  $\text{AcOH}$ - $\text{EtOH}$ . After addition of the whole amount of 5%  $\text{Na-Hg}$ , the mixture was heated at 60 °C for 4 h. The Hg metal formed was removed by decantation and the mother liquor was evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution was made acidic with conc.  $\text{HCl}$ , and then washed with  $\text{Et}_2\text{O}$ . The organic layer was extracted with 10%  $\text{HCl}$  aq. The acidic aqueous layer was combined with the washings and the whole was made alkaline with 15%  $\text{KOH}$  aq., then extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on  $\text{Al}_2\text{O}_3$  (basic, grade I) with benzene followed by  $\text{CHCl}_3$  to give colorless needles<sup>35)</sup> (0.76 g), mp 159–162 °C, which were recrystallized from  $\text{MeOH}$ . *Anal.* Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_5$ : C, 66.85; H, 5.61; N, 4.10. Found: C, 66.59; H, 5.62; N, 4.08. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3370 (NH).  $^1\text{H-NMR}$   $\delta$ : 1.47 (2H, s,  $\text{NH}_2$ ), 1.60–2.30 (2H, m,  $\text{C}_3$ - $\text{H}_2$ ), 2.75–2.95 (2H, m,  $\text{C}_4$ - $\text{H}_2$ ), 3.30–3.60 (1H, m,  $\text{C}_2$ -H), 3.75 (3H, s,  $\text{OCH}_3$ ), 4.07 (1H, d,  $J=5.1$  Hz,  $\text{C}_1$ -H), 5.88 and 5.91 (each 2H, s,  $\text{OCH}_2\text{O}$ ), 6.55, 6.58, 6.72, and 6.78 (each 1H, s, arom. H).

**Formylation of the 2-Methoxy-4,5-methylenedioxy-amine (3d) [1-Formamido-2-(2-methoxy-4,5-methylene-**



**dioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (2d)]**—A solution of the amine (3d) (0.20 g) in  $\text{HCONH}_2$  (2 ml) was heated at  $140^\circ\text{C}$  for 3 h. The mixture was poured into ice-water. The precipitate was collected by filtration and purified by column chromatography on  $\text{Al}_2\text{O}_3$  with benzene to give colorless needles (0.15 g), mp  $210\text{--}215^\circ\text{C}$ . *Anal.* Calcd for  $\text{C}_{20}\text{H}_{19}\text{NO}_6$ : C, 65.03; H, 5.19; N, 3.79. Found: C, 64.55; H, 5.24; N, 3.72. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3360 (NH), 1665 (CO).  $^1\text{H-NMR}$   $\delta$ : 1.76—2.10 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.70—3.00 (2H, m,  $\text{C}_4\text{-H}_2$ ), 3.35—3.70 (1H, m,  $\text{C}_2\text{-H}$ ), 3.78 and 3.81 (total 3H, s,  $\text{OCH}_3$ ), 5.54 (1H, d,  $J=4.5$  Hz,  $\text{C}_1\text{-H}$ ), 5.61 (1H, br s, NH), 5.88 (4H, s,  $\text{OCH}_2\text{O} \times 2$ ), 6.50—6.78 (4H, m, arom. H  $\times 4$ ), 7.89 (1H, s, NCHO).

**2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2H)-one Oxime (The 5-Methoxy-2,3-methylenedioxy-oxime) (4e)**—A mixture of the tetralone<sup>1b)</sup> (1e) (3.00 g),  $\text{NH}_2\text{OH} \cdot \text{HCl}$  (4.29 g), and pyridine (4.29 ml) in EtOH (17.3 ml) was refluxed for 3.5 h. After cooling, the mixture was diluted with water (80 ml) and the precipitate formed was collected by filtration. The precipitate was washed with 5% HCl aq., then 5%  $\text{NaHSO}_3$  aq., and water. Recrystallization of the precipitate from  $\text{CHCl}_3\text{--EtOH}$  gave colorless needles (2.91 g), mp  $212\text{--}215^\circ\text{C}$ . *Anal.* Calcd for  $\text{C}_{19}\text{H}_{17}\text{NO}_6$ : C, 64.22; H, 4.82; N, 3.94. Found: C, 64.05; H, 4.84; N, 3.84. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3250 (OH).

**Reduction of the 5-Methoxy-2,3-Methylenedioxy-oxime (4e) with Sodium Amalgam [2-(5-Methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-naphthylamine (The 5-Methoxy-2,3-methylenedioxy-amine) (3e)]**—Sodium amalgam (5%) (302 g) was added portionwise to a suspension of the oxime (4e) (2.00 g) in abs. EtOH (302 ml) at  $60^\circ\text{C}$ . During addition of the amalgam, the reaction mixture was kept slightly acidic by addition of 50% AcOH—EtOH. After completion of addition of the reagent, the mixture was heated at  $60^\circ\text{C}$  for 4 h. When the reaction was complete, the resulting precipitate (Hg metal and AcONa) was collected by filtration and washed with hot MeOH. The filtrate and washings were combined, neutralized with sat.  $\text{NaHCO}_3$  aq., and evaporated to dryness *in vacuo*. The residue was dissolved in water, and the solution was made alkaline with 5% NaOH aq., then extracted with  $\text{CHCl}_3$ . The chloroform solution was washed with sat. NaCl aq., dried over  $\text{K}_2\text{CO}_3$ , and evaporated to dryness *in vacuo*. The residue was chromatographed on  $\text{Al}_2\text{O}_3$  (basic, grade II) with benzene followed by  $\text{CHCl}_3$ . The eluates with benzene and with  $\text{CHCl}_3$  gave colorless prisms (1.54 g), mp  $139\text{--}162^\circ\text{C}$ , which were recrystallized from EtOH. *Anal.* Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_5$ : C, 66.85; H, 5.61; N, 4.10. Found: C, 66.60; H, 5.71; N, 4.14. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3375 and 3325 (NH).  $^1\text{H-NMR}$   $\delta$ : 1.56 (2H, s,  $\text{NH}_2$ ), 1.80—2.20 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.60—3.00 (3H, m,  $\text{C}_2\text{-H}$  and  $\text{C}_4\text{-H}_2$ ), 3.72 (3H, dif. s,  $\text{OCH}_3$ ), 4.04 (1H, dif. d,  $J=ca. 10.0$  Hz,  $\text{C}_1\text{-H}$ ), 5.86 (4H, s,  $\text{OCH}_2\text{O} \times 2$ ), 6.19 (*ca.* 2/3H, d,  $J=2.5$  Hz, *trans*- $\text{C}_4\text{-}$  or *trans*- $\text{C}_6\text{-H}$ ), 6.23 (*ca.* 1/3H, d,  $J=2.5$  Hz, *cis*- $\text{C}_4\text{-}$  or *cis*- $\text{C}_6\text{-H}$ ), 6.37 (1H, dif. d,  $J=ca. 2.5$  Hz,  $\text{C}_6\text{-}$  or  $\text{C}_4\text{-H}$ ), 6.52 (1H, s,  $\text{C}_5\text{-H}$ ), 6.76 (1/3H, s, *cis*- $\text{C}_8\text{-H}$ ), 7.14 (2/3H, s, *trans*- $\text{C}_8\text{-H}$ ).

**Formylation of the 5-Methoxy-2,3-methylenedioxy-amine (3e) [1-Formamido-2-(5-methoxy-2,3-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene (The 5-Methoxy-2,3-methylenedioxy-formamide) (2e)]**—A mixture of the amine (3e) (0.14 g) and  $\text{HCONH}_2$  (1.36 g) was heated at  $140^\circ\text{C}$  for 3 h. After cooling, the mixture was poured into ice-water (20 ml). The precipitate was collected by filtration and recrystallized from benzene to give colorless needles (0.089 g), mp  $180\text{--}185^\circ\text{C}$ . *Anal.* Calcd for  $\text{C}_{20}\text{H}_{19}\text{NO}_6$ : C, 65.03; H, 5.19; N, 3.79. Found: C, 65.35; H, 5.22; N, 3.74. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3225 (NH), 1678 and 1648 (CO); IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3420 (NH), 1690 (CO).  $^1\text{H-NMR}$   $\delta$ : 1.90—2.30 (2H, m,  $\text{C}_3\text{-H}_2$ ), 2.60—3.40 (3H, m,  $\text{C}_2\text{-H}$  and  $\text{C}_4\text{-H}_2$ ), 3.69 (3H, dif. s,  $\text{OCH}_3$ ), 5.32—5.65<sup>36)</sup> (2H, m, NH and  $\text{C}_1\text{-H}$ ), 5.84 (4H, dif. s,  $\text{OCH}_2\text{O} \times 2$ ), 6.10 (*ca.* 5/9H, d,  $J=2.0$  Hz, *cis*- $\text{C}_4\text{-}$  or *cis*- $\text{C}_6\text{-H}$ ), 6.18 (*ca.* 4/9H, d,  $J=2.0$  Hz, *trans*- $\text{C}_4\text{-}$  or *trans*- $\text{C}_6\text{-H}$ ), 6.34 (1H, m,  $\text{C}_6\text{-}$  or  $\text{C}_4\text{-H}$ ), 6.55 and 6.74 (each 1H, m,  $\text{C}_5\text{-}$  and  $\text{C}_8\text{-H}$ ), 7.92 (*ca.* 5/9H, s, *cis*-NCHO), 8.10 (*ca.* 4/9H, s, *trans*-NCHO).

**Catalytic Reduction of the Trimethoxy-oxime (4a) with Raney Nickel [A Diastereomeric Mixture of the Trimethoxy-amines (3a)]**—A solution of the trimethoxy-oxime (4a) (0.25 g) in abs. EtOH (2 ml) was hydrogenated over Raney Ni (*ca.* 0.1 g) at room temperature under atmospheric pressure for 12 h. The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from  $\text{CHCl}_3\text{--cyclohexane}$  gave colorless pillars (0.09 g), mp  $143\text{--}148^\circ\text{C}$ . This material (*cis:trans*=7:1) was essentially identical with the trimethoxy-amine (3a) described above.

**6,7-Methylenedioxy-2-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one Hydrazone (The Trimethoxy-hydrazone) (15)**—A mixture of the trimethoxy-tetralone (1a) (0.51 g),  $\text{EtOCH}_2\text{CH}_2\text{OH}$  (7 ml), 80%  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$  (3.2 ml), and  $\text{Et}_3\text{N}$  (2 ml) was refluxed for 12 h. When the reaction was completed, the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in  $\text{CHCl}_3$ , and the solution was washed with water, dried over  $\text{K}_2\text{CO}_3$ , then evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH— $\text{Et}_2\text{O}$  gave colorless prisms (0.46 g), mp  $138\text{--}140^\circ\text{C}$ . *Anal.* Calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_5$ : C, 64.85; H, 5.99; N, 7.56. Found: C, 64.54; H, 5.92; N, 7.42. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3370 and 3220 (NH).  $^1\text{H-NMR}$   $\delta$ : 1.80—2.72 (4H, m,  $\text{C}_3\text{-}$  and  $\text{C}_4\text{-H}_2$ ), 3.76 (6H, s,  $\text{OCH}_3 \times 2$ ), 3.80 (3H, s,  $\text{OCH}_3$ ), 4.00—4.16 (1H, m,  $\text{C}_2\text{-H}$ ), 5.12 (2H, br s,  $\text{NH}_2$ ), 5.90 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.39 (2H, s,  $\text{C}_2\text{-}$  and  $\text{C}_6\text{-H}$ ), 6.52 (1H, s,  $\text{C}_5\text{-H}$ ), 7.54 (1H, s,  $\text{C}_8\text{-H}$ ).

**Catalytic Hydrogenation of the Trimethoxy-hydrazone (15) over Platinum Oxide in Acetic Acid [The *cis*-Trimethoxy-amine (*cis*-3a)]**—A solution of the hydrazone (15) (0.50 g) in AcOH (25 ml) was hydrogenated over  $\text{PtO}_2 \cdot 1\text{--}3 \text{ H}_2\text{O}$  (0.065 g) at room temperature under atmospheric pressure. After the catalyst had been removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water, and the solution was made alkaline with 10% NaOH aq., then extracted with  $\text{Et}_2\text{O}$ . The ethereal solution was dried over  $\text{K}_2\text{CO}_3$  and



evaporated to dryness. Recrystallization of the residue from EtOH–Et<sub>2</sub>O gave colorless prisms (0.37 g), mp 148–151 °C, which were identical with the *cis*-trimethoxy-amine (*cis*-**3a**) described above.

**Trial Catalytic Reduction of the Trimethoxy-hydrazone (15) over 10% Palladium-carbon**—A solution of the hydrazone (**15**) (0.12 g) in EtOH (5 ml) containing 6 N HCl aq. (0.2 ml) was hydrogenated over 10% Pd-C (0.046 g) at room temperature under atmospheric pressure until absorption of hydrogen ceased. The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. p-TLC of the residue on SiO<sub>2</sub> with benzene–AcOEt (3 : 1, v/v) gave colorless needles (0.046 g), mp 118–121 °C, which were recrystallized from MeOH. This material was identical with a sample of the trimethoxy-stilbene (**5a**).

#### References and Notes

- 1) a) This work was presented in part at the 16th Symposium on The Chemistry of Natural Products, Osaka, October 1972 [H. Ishii, T. Deushi, and K.-I. Harada, Symposium Papers, p. 327]; b) Part I: H. Ishii, E. Kawanabe, K.-I. Harada, T. Deushi, E. Ueda, T. Watanabe, Y.-I. Ichikawa, M. Sakamoto, T. Ishida, T. Takahashi, K. Nakajima, and T. Ishikawa, *Chem. Pharm. Bull.*, **31**, 3039 (1983).
- 2) a) For a review of the chemistry of these alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. 4, ed. by R. H. F. Manske, Academic Press, New York-London, 1954, p. 253; R. H. F. Manske, *ibid.*, Vol. 7, 1959, p. 430; R. H. F. Manske, *ibid.*, Vol. 10, 1968, p. 485; F. Šantavý, *ibid.*, Vol. 12, 1970, p. 417; V. Preininger, *ibid.*, Vol. 15, 1975, p. 241; F. Šantavý, *ibid.*, Vol. 17, 1979, p. 493; H. Ishii and T. Ishikawa, *Yakugaku Zasshi*, **101**, 663 (1981); b) For antileukemic activity, see M. E. Wall, M. C. Wani, and Y. L. Taylor, Abstracts, 162nd National Meeting of the American Chemical Society, Washington D.C., Sept. 1971, MEDI 34; Abstracts of the Third International Congress of Heterocyclic Chemistry: B, Sendai, Japan, 1971, p. 29; W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojánek, *J. Pharm. Sci.*, **61**, 1858 (1972); F. R. Stermitz, K. A. Larson, and D. K. Kim, *J. Med. Chem.*, **16**, 939 (1973).
- 3) a) A. S. Bailey, R. Robinson, and R. S. Staunton, *J. Chem. Soc.*, **1950**, 2277; b) T. Richardson, R. Robinson, and E. Seijo, *ibid.*, **1937**, 835; c) A. S. Bailey and R. Robinson, *ibid.*, **1950**, 1375; A. S. Bailey and C. R. Worthing, *ibid.*, **1956**, 4535.
- 4) a) K. W. Gopinath, T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *J. Chem. Soc.*, **1957**, 4760; b) K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Tetrahedron*, **14**, 322 (1961); c) H. R. Arthur and Y. L. Ng, *J. Chem. Soc.*, **1959**, 4010; K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan, *ibid.*, **1959**, 4012; K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.*, **10**, 85, 867 (1973).
- 5) T. Kametani, K. Kigasawa, M. Hiiragi, O. Kusama, E. Hayashi, and H. Ishimaru, *Chem. Pharm. Bull.*, **19**, 1150 (1971).
- 6) T. Kametani, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Heterocycl. Chem.*, **10**, 31 (1973).
- 7) This compound melted at 91–103 °C once and crystallized again to give colorless needles, mp 161–173 °C.
- 8) J. Slavík and L. Slavíková, *Collect. Czech. Chem. Commun.*, **20**, 21 (1955); J. Slavík, *ibid.*, **20**, 198 (1955); J. Slavík and L. Slavíková, *ibid.*, **25**, 1667 (1960); J. Slavík, L. Dolejš, V. Hanuš, and A. D. Cross, *ibid.*, **33**, 1619 (1968); J. Slavík, and F. Šantavý, *ibid.*, **37**, 2804 (1972); C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 755 (1962); M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nôgeikagaku Kaishi*, **39**, 168 (1965); M. Onda, K. Abe, K. Yonezawa, N. Esumi, and T. Suzuki, *Chem. Pharm. Bull.*, **18**, 1435 (1970); H. Ishii, K.-I. Harada, T. Ishida, E. Ueda, K. Nakajima, I. Ninomiya, T. Naito, and T. Kiguchi, *Tetrahedron Lett.*, **1975**, 319; H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K.-I. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Pharm. Bull.*, **26**, 864 (1978).
- 9) H. R. Arthur, W. H. Hui, and Y. L. Ng, *J. Chem. Soc.*, **1959**, 4007.
- 10) T. Masamune, M. Ohno, M. Koshi, S. Ohuchi, and T. Iwadare, *J. Org. Chem.*, **29**, 1419 (1964).
- 11) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, **1954**, 3045.
- 12) a) S. v. Kostanecki and V. Lampe, *Chem. Ber.*, **41**, 1327 (1908); b) F. W. Semmler, *ibid.*, **41**, 1768 (1908).
- 13) N. K. Clauson-Kaas, *Acta Chem. Scand.*, **9**, 1 (1955).
- 14) Our conclusion was accepted by Prof. Kametani (private communication).
- 15) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
- 16) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, **1962**, 470.
- 17) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 575 (1958).
- 18) The catalytic hydrogenation of the hydrazone (**15**) over 10% palladium-charcoal in acetic acid or platinum oxide in ethanol did not take place.
- 19) One of these 5H signals which were assigned as aromatic protons should be the signal of the C<sub>4</sub>-H olefinic proton.
- 20) After addition of D<sub>2</sub>O, the signal changed to a doublet (*J* = 10.0 Hz).
- 21) When measured at 140 °C, these changed to sharp signals at  $\delta$  6.66 (1H, s) and 6.72 (1H, s).
- 22) After addition of D<sub>2</sub>O, the signal changed to a doublet (*J* = 4.5 Hz).
- 23) When measured at 140 °C, these changed to sharp signals at  $\delta$  6.59 (2H, s), 6.68 (1H, s), and 6.74 (1H, s).

- 24) Recrystallization of the precipitate from EtOH gave the amine·HCl salt, mp 222—225 °C.
- 25) The precipitate melted at 222—230 °C.
- 26) After addition of D<sub>2</sub>O, the signal changed to a doublet ( $J=10.0$  Hz).
- 27) After addition of D<sub>2</sub>O, this signal changed to two doublets ( $J=8.0$  and  $5.0$  Hz) which can be ascribed to the *trans*- and the *cis*- isomers, respectively.
- 28) These signals were observed as two sharp singlets and their total intensity corresponded to 6 H.
- 29) In this region, the aromatic signals were observed as seven peaks which were relatively sharp.
- 30) After addition of D<sub>2</sub>O, the signals due to C<sub>1</sub> protons were clearly observed as a diffused doublet ( $J=ca. 8.0$  Hz) at  $\delta$  5.28 and a relatively sharp doublet ( $J=5.0$  Hz) at  $\delta$  5.42 with disappearance of the NH signal.
- 31) The signal due to C<sub>4</sub> protons overlapped with the signal of dimethyl sulfoxide (DMSO).
- 32) After addition of D<sub>2</sub>O, the signals due to C<sub>1</sub> protons were clearly observed as two doublets at  $\delta$  5.28 (d,  $J=10.0$  Hz, *trans*) and at  $\delta$  5.42 ( $J=5.0$  Hz, *cis*) with disappearance of the NH signal.
- 33) After addition of D<sub>2</sub>O, the signal due to the C<sub>1</sub> proton was observed as a sharp doublet ( $J=5.0$  Hz) at  $\delta$  5.42 with disappearance of the NH signal.
- 34) After addition of D<sub>2</sub>O, the signals due to C<sub>1</sub> protons were clearly observed as two sharp doublets at  $\delta$  5.47 ( $J=10.0$  Hz, *trans*) and at  $\delta$  5.60 ( $J=4.5$  Hz, *cis*).
- 35) Since the <sup>1</sup>H-NMR spectra of the purified sample itself and of its formylated product (**2d**) were rationalized in terms of the *cis*-isomer, the sample purified by recrystallization was supposed to be the *cis*-isomer (*cis*-**3d**). However, the crude product showed data indicative of a mixture of diastereomeric isomers on TLC and in the <sup>1</sup>H-NMR spectrum.
- 36) After addition of D<sub>2</sub>O, the signals due to C<sub>1</sub> protons were clearly observed as two sharp doublets at  $\delta$  5.48 ( $J=10.0$  Hz, *trans*) and at  $\delta$  5.60 ( $J=5.0$  Hz, *cis*).