*Anal.* Calcd for $C_{13}H_{11}BrN_2O_2S$: C, 46.03; H, 3.26; N, 8.25. Found: C, 46.12; H, 3.9; N, 8.38.

**4-Keto-2-thio-8-acetoxymethyl-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (19).**—A stirred suspension of 4-keto-2-thio-8-bromomethyl-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**18**) (3.0 g, 8.9 mmol) and AgOAc (1.6 g, 10 mmol) in 30 ml of HOAc was refluxed 1.25 hr and the solid filtered. The filtrate was concentrated *in vacuo* and added to 50 ml of $H_2O$ which was made acidic (10% HCl). The precipitate was collected to yield **19** (1.5 g, 52%), mp 202–204° (EtOAc–$Me_2CO$); the spectral data are consistent with the assigned structure.

*Anal.* Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79. Found: C, 56.35; H, 4.52; N, 8.79.

**4-Keto-2-thio-8-methylene-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (20).**—A stirred solution of 4-keto-2-thio-8-bromomethyl-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (**18**) (4.00 g, 11.8 mmol) and NaOBz (1.87 g, 13.0 mmol) in 10 ml of DMF was refluxed 5 hr, cooled, and poured into 200 g of crushed ice. The suspension was made acidic (10% HCl) and the precipitate collected and decolorized with activated charcoal in $Me_2CO$. The $Me_2CO$ was removed *in vacuo* to yield **20** (0.5 g, 16.4%), mp 186–187° ($Me_2CO$); the spectral data were consistent with the assigned structure.

*Anal.* Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84. Found: C, 60.07; H, 3.74; N, 10.54.

**2,4-Diketo-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).**—A stirred solution of *N*-(2-hydroxyethyl)-5-phenylbarbituric acid (**4**) (10.0 g, 0.04 mol) in 100 ml of 32% HBr–HOAc (Eastman) was refluxed overnight in a stoppered Wheaton glass pressure bottle. The HOAc was removed *in vacuo* and the residue added to 400 ml of crushed ice. The $H_2O$ was decanted and the gummy residue crystallized to yield **21** (4.25 g, 46.2%), mp 267–268° ($Me_2CO$); the spectral data are consistent with the assigned structure.

*Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.37; N, 12.16. Found: C, 62.46; H, 4.48; N, 12.15.

**2,4-Diketo-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.4.0]decane (22).**—A solution of *N*-(3-bromopropyl)-5-phenylbarbituric acid (**5**) (1.0 g, 3.0 mmol) in 30 ml of $C_5H_5N$ was stirred 3 days and then concentrated *in vacuo*. The residue was dissolved in 10 ml of $H_2O$ and the solution made acidic (10% HCl). The precipitate was collected to yield **22** (400 mg, 54.6%), mp 290.5–291.5 dec ($Me_2CO$); the spectral data are consistent with the assigned structure.

*Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 64.15; H, 5.03; N, 11.57.

**$\alpha$-Phenylacetamide (23). A. Hydrolysis of 4-Keto-2-thio-8-bromomethyl-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (18).**—A solution of **18** (3.0 g, 8.8 mmol) in 10 ml of 58% $NH_4OH$ and 20 ml of 21% $(NH_4)_2S$ was maintained at 150° in a steel reaction vessel for 3 days. The solvent was removed *in vacuo* and the residue dissolved in $CHCl_3$, decolorized (activated charcoal), dried ($MgSO_4$), and evaporated to yield **23** (0.30 g, 26%), mp 154–155° ($CHCl_3$–$Et_2O$) (lit.[5] mp 154–155°). The spectral data were identical with those for $\alpha$-phenylacetamide.[6]

**B. Hydrolysis of 2,4-Diketo-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]nonane (21).**—The procedure utilized was identical with that in A. Compound **23**, mp 151–152° ($CHCl_3$–$Et_2O$), was obtained.

**C. Hydrolysis of 2,4-Diketo-5-phenyl-$\Delta^5$-7-oxa-1,3-diazabicyclo[4.3.0]decane (22).**—The procedure utilized was identical with that in A and B. Compound **23**, mp 154–155 ($CHCl_3$–$Et_2O$), was obtained.

**Registry No.**—**8**, 30345-98-3; **9**, 30345-99-4; **14**, 30346-00-0; **15**, 30346-01-1; **16**, 30346-02-2; **17**, 30346-03-3; **18**, 30409-27-9; **19**, 30346-04-4; **20**, 30346-05-5; **21**, 30346-06-6; **22**, 30349-28-0.

**Acknowledgment.**—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grants GM-09254 and GM-01341. We appreciate the assistance rendered by Mr. Darrell Abernethy in the preparation of starting materials.

(5) "The Merck Index," 7th ed, Merck and Co., Inc., Rahway, N. J., 1960, p 799.

(6) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1970, Prism No. 2236, nmr no. 6588.

# The Synthesis of the Thalictrum Alkaloids, Adiantifoline and Thalicsimidine[1]

RAYMOND W. DOSKOTCH,* J. D. PHILLIPSON,[2] A. B. RAY, AND JACK L. BEAL

*Division of Natural Products Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210*

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A total synthesis is described for adiantifoline (**1**) involving, in the final step, the joining by the Ullmann reaction of the two components (+)-(*S*)-6′-bromolaudanosine (**12**) and (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), thus establishing the structure for the alkaloid. The aporphine intermediate **4** was formed by two routes, both leading to the same Pschorr cyclization reactant, 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**). One pathway started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxyphenylacetamide (**5**) with the nitro group being introduced to the tetrahydroisoquinoline **7**, while the other procedure started with *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxy-6′-nitrophenylacetamide (**9**). Only polyphosphoric ester was successful in cyclizing compound **9** in the Bischler–Napieralski reaction. Methylation of compound **4** to (+)-(*S*)-1,2,3,9,10-pentamethoxyaporphine (**13**) or thalicsimidine constitutes its total synthesis and confirms its structure earlier assigned on the basis of spectroscopic evidence. Four pentaoxygenated benzyltetrahydroisoquinolines, **14–17**, were obtained from intermediates in the synthesis.

Adiantifoline, the fourth member of a novel group dimeric benzylisoquinoline–aporphine alkaloids, was isolated from *Thalictrum minus* L. var. *adiantifolium* Hort., and was assigned structure **1** from physical and chemical evidence.[3] A confirmation of this structure was necessary and was obtained by a total synthesis of (+)-adiantifoline,[4] since scarcity of the alkaloid precluded further degradative studies and the evidence at hand was also consistent with structure **2**. In addition, a quantity of the alkaloid could now be made available for pharmacological testing,[5] which otherwise would not have been possible.

(1) Alkaloids of Thalictrum. XII. Paper XI: R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Lloydia*, **32**, 29 (1969). This investigation was supported by Public Health Service research grants HE-07502 and FR-00328, the latter for purchase of a Varian A-60A nmr spectrometer with accessories.

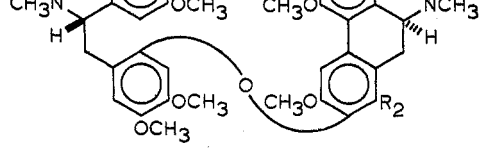
(2) Acknowledges with thanks the receipt of a Wellcome Research Travel Grant. Permanent address: Department of Pharmacy, Chelsea College, University of London, London, United Kingdom.

(3) (a) R. W. Doskotch, P. L. Schiff, Jr., and J. L. Beal, *Tetrahedron Lett.*, 4999 (1968). (b) The isolation procedure is found in paper XI.[1]

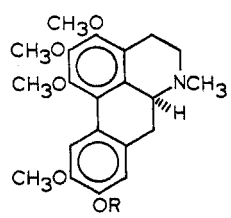
(4) A preliminary report of this work has appeared: R. W. Doskotch, J. D. Phillipson, A. B. Ray, and J. L. Beal, *Chem. Commun.*, 1083 (1969).

(5) Testing for antitumor activity will be of special interest because of the success thalicarpine (**3**) has been having in the evaluation program of the Cancer Chemotherapy National Screening Center; see R. E. Perdue and J. L. Hartwell, *Morris Arbor. Bull.*, **20**, 35 (1969).

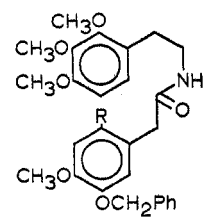
Since the proposed structure for adiantifoline differs from that of thalicarpine (**3**) by the presence of one additional methoxyl group, the general route for its synthesis was patterned after the successful one for thalicarpine,[6] in which the suitable benzyltetrahydroisoquinoline and aporphine portions were in the final step joined *via* the Ullmann reaction. The required aporphine, (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), for adiantifoline was prepared starting with 2,3,4-trimethoxyphenylethylamine[7] and 3-benzyloxy-4-methoxyphenylacetic acid[8] as the acid chloride. The Schotten–Baumann condensation product, *N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoyxphenylacetamide (**5**), was cyclized under conditions of the Bischler–Napieralski reaction and the unstable imine product was quickly reduced to 1-(3′-benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and isolated as the hydro-



**1**, $R_1$ = $OCH_3$; $R_2$ = H
**2**, $R_1$ = H; $R_2$ = $OCH_3$
**3**, $R_1$ = $R_2$ = H



**4**, R = H
**13**, R = $CH_3$

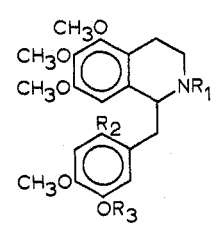


**5**, R = H
**9**, R = $NO_2$

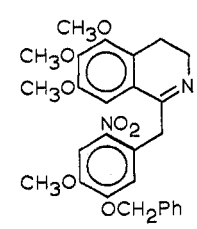
chloride salt. N-Methylation of compound **6** by formaldehyde and sodium borohydride gave 1-(3′-benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**7**) which on nitration according to the conditions of Shamma and Slusarchyk[9] yielded the 6′-nitro compound **8**. The assigned position of nitration was supported: first, by the nmr spectrum of the nitro product, since the aromatic region—excluding the protons of the benzyloxy group—showed three one-proton singlets at $\delta$ 6.25, 6.57, and 7.54; second, by the nmr spectrum of the eventual aporphine product (racemic **4**) which exhibited a one-proton singlet downfield at $\delta$ 7.96, a position unique for $H_{11}$ protons,[10] and in agreement with the predicted product; and third, by the formation (*vide infra*) of 1-(3′-benzyloxy-4′-methoxybenzyl-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**) *via* an alternate unambiguous route through the nitroamide **9**.

The Pschorr reaction product, 1,2,3,10-tetramethoxy-9-hydroxyaporphine (racemic **4**), was obtained from the nitroamine **8** through the reduction product, 1-(3′-benzyloxy-4′-methoxy-6′-aminobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**), and, under the conditions of cyclization, the benzyloxy group was, in addition, summarily removed. Resolution of the racemic aporphine **4** was accomplished by fractional crystallization of the di-*p*-toluoyl (+)-tartarate salts yielding the diastereoisomer with the (+)-(*S*)-aporphine enantiomer **4** as the least soluble salt, after first removal of part of the (−)-(*R*) enantiomer with di-*p*-toluoyl-(−)-tartaric acid. The Ullmann condensation of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**) with (+)-(*S*)-6′-bromolaudanosine (**12**)[11] afforded adiantifoline (**1**) in a yield of 21% after chromatography of the reaction mixture. Comparison of the synthetic compound with the natural product was made by the examination of the ir, uv, and nmr spectra, CD curves, tlc characteristics, and mixture melting points. No distinguishing characteristics were noted.

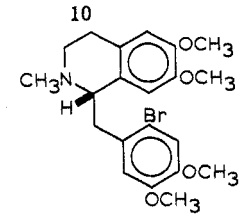
Another synthetic route leading to the aporphine **4** was developed in which the nitro group necessary for the Pschorr cyclization was introduced early in the sequence. The nitroamide **9** was prepared from 3-benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone[12] and 2,3,4-trimethoxyphenylethylamine[7] *via* the Arndt–Eistert method. Cyclization of the nitroamide **9** in the Bischler–Napieralski reaction could not be accomplished by the use of the usual condensation reagents under a variety of conditions,[13] but, with polyphosphoric ester prepared according to Cava, *et al.*,[14] a moderate yield of 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-didhydroisoquinoline (**10**) was realized. Reaction of the cyclization product **10** with methyl iodide gave the quaternary methiodide which on reduction with sodium borohydride formed 1-(3′-benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**) identical with the nitration product from 1-(3′-benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**7**). In practice, this



**6**, $R_1$ = $R_2$ = H; $R_3$ = benzyl
**7**, $R_1$ = $CH_3$; $R_2$ = H; $R_3$ = benzyl
**8**, $R_1$ = $CH_3$; $R_2$ = $NO_2$; $R_3$ = benzyl
**11**, $R_1$ = $CH_3$; $R_2$ = $NH_2$; $R_3$ = benzyl
**14**, $R_1$ = $R_2$ = $R_3$ = H
**15**, $R_1$ = $CH_3$; $R_2$ = $R_3$ = H
**16**, $R_1$ = $R_2$ = H; $R_3$ = $CH_3$
**17**, $R_1$ = $R_3$ = $CH_3$; $R_2$ = H



**10**



**12**

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(12) M. Tomita and I. Kikkawa, *Chem. Pharm. Bull. (Tokyo)*, **4**, 230 (1956).
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second route results in a higher overall yield of the aporphine **4**, since it eliminates the nitration of the benzyltetrahydroisoquinoline **7**, which was found to give unexplained inconsistent yields.

Thalicsimidine, an alkaloid from *Thalictrum simplex* L., was assigned the structure of (+)-(*S*)-1,2,3,9,-10-pentamethoxyaporphine (**13**) on the basis of physical evidence.[15] Methylation of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**) with diazomethane gave the pentamethoxyaporphine **13** which possessed physical properties (melting point, $[\alpha]_D$, and uv, ir, and nmr spectra) in agreement with those reported for thalicsimidine. This synthesis, therefore, substantiates the suggested structure and, in addition, constitutes the total synthesis of this alkaloid.

Having on hand the pentaoxygenated benzylisoquinolines, 1-(3′-benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and its N-methyl derivative **7**, allowed us to prepare 1-(3′-hydroxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**14**), its N-methyl derivative **15**, and 1-(3′,4′-dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**16**) and its N-methyl derivative **17**. To our knowledge, alkaloids possessing these structures have as yet not been discovered. We record their properties for value in characterization, as it is very likely that they will be discovered in the future.

## Experimental Section[16]

***N*-(2,3,4-trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxyphenylacetamide (5).**—Thionyl chloride (8 ml) was added to 3-benzyloxy-4-methoxyphenylacetic acid[8] (11 g) in 30 ml of dry benzene and the mixture was heated for 3 hr at 50° under anhydrous conditions. The beige-colored acid chloride remaining, after removal of the volatiles by evaporation of the reaction mixture at reduced pressure, was dissolved in 50 ml of dry ether and added dropwise to a well-stirred mixture of 2,3,4-trimethoxyphenylethylamine[7] hydrochloride (10 g) in 200 ml of 5% aqueous NaOH and 300 ml of ether. After stirring 1 hr at room temperature, the mixture was extracted with $CHCl_3$ and the extract was washed with $H_2O$, dilute HCl, and $H_2O$ and then dried ($Na_2SO_4$). The thick oil left after evaporation of the solvent crystallized from ether–chloroform as colorless needles of **5** (18.0 g): mp 104–105°; ir 3410 (NH) and 1655 $cm^{-1}$ (amide C=O).

*Anal.* Calcd for $C_{27}H_{31}NO_6$: C, 69.68; H, 6.67; N, 3.22. Found: C, 69.74; H, 6.77; N, 3.29.

**1-(3′-Benzyloxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (6).**—Amide **5** (5 g) in 50 ml of dry benzene and 5 ml of $POCl_3$ were heated at 80° for 1 hr, under nitrogen. The brown residue left after evaporation of the mixture was triturated twice with petroleum ether, then dissolved in 50 ml of acetone, and diluted with 200 ml of 2% aqueous HCl. The aqueous solution was washed twice with ether, cooled (ice), basified with dilute $NH_4OH$, and rapidly extracted with ether. The washed ($H_2O$) and dried ($Na_2SO_4$) ether solution was evaporated and the residue (imine) was dissolved in 50 ml of $CH_3OH$, cooled (ice), and treated with 2.2 g of $NaBH_4$ over a 0.5-hr period while stirring. After 2 hr the residue remaining on evaporation of the solvent was treated with $H_2O$ and extracted with ether. The residue from the ether solution gave from ether–95% ethanol the crystalline hydrochloride of **6** as needles (3.6 g): mp 118–119°; uv max 282 mμ (log ε 3.71).

*Anal.* Calcd for $C_{27}H_{32}NO_5Cl \cdot H_2O$: C, 64.35; H, 6.75; N, 2.78. Found: C, 64.77; H, 6.84; N, 2.95.

**1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (7).**—The amine **6** (generated from 4.8 g of the HCl salt) in 150 ml of $CH_3OH$ was stirred at room temperature with 40 ml of 37% formalin for 0.5 hr, then cooled (ice), and treated with 7.5 g of $NaBH_4$ over 0.5 hr. After stirring an additional 2 hr, the reaction mixture was evaporated to dryness, treated with $H_2O$, and extracted with ether. The ether-soluble residue after forming the hydrochloride gave from ether–methanol the crystalline salt of **7** (4.7 g): mp 123–125°; uv max 282 mμ (log ε 3.66).

*Anal.* Calcd for $C_{28}H_{34}NO_5Cl$: C, 67.34; H, 6.81; N, 2.81; Cl, 7.10. Found: C, 67.22; H, 6.98; N, 2.86; Cl, 7.17.

**1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-2-methyl-5,6,7trimethoxy-1,2,3,4-tetrahydroisoquinoline (8). A. By Nitration of 7.**—To compound **7** (liberated from 4.2 g of the HCl salt) frozen in 20 ml of glacial HOAc was added ice-cold concentrated $HNO_3$ (7.5 ml) in five equal portions. After the first portion was added, the frozen mixture was liquified by crushing and vigorous stirring. The completed reaction mixture was poured onto crushed ice, basified with $NH_4OH$, and extracted with $CHCl_3$. The red oil remaining after evaporation of the dried ($K_2CO_3$) $CHCl_3$ solution was treated with 10 ml absolute EtOH followed by an ethereal HCl solution until precipitation was complete. The beige solid was crystallized from ether–methanol to give 3.2 g of the hydrochloride **8**, mp 129–131°.

**B. From the Nitroimine 10.**—A solution of the nitroimine **10** (492 mg) in 20 ml of $CH_3OH$, and 2 ml of $CH_3I$ was refluxed for 24 hr. The cooled solution deposited an oil which solidified as pale yellow prisms of the methiodide, mp 159–160°. The reaction mixture was evaporated to dryness at reduced pressure. The crystalline residue was dissolved in 20 ml of $CH_3OH$ and then treated with 0.2 g of $NaBH_4$ in small portions over 0.5 hr and the reaction was allowed to proceed overnight. The residue remaining on removal of the solvent was taken up in water and extracted with ether. The dried ($Na_2SO_4$) ether extract left a residue (0.41 g) that formed the crystalline hydrochloride of **8**, mp 129–131°.

*Anal.* Calcd for $C_{28}H_{33}N_2O_7Cl$: C, 61.70; H, 6.06; N, 5.14. Found: C, 61.54; H, 6.11; N, 5.17.

**1-(3′-Benzyloxy-4′-methoxy-6′-aminobenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (11).**—The base **8** (liberated from 5.5 g of the HCl salt) in ice-cold 60% aqueous HOAc (120 ml) was stirred and treated with 10 g of zinc dust over a period of 5 min. Stirring was continued until an almost colorless solution formed and then the zinc was removed by filtration. The ice-cold filtrate was basified with $NH_4OH$ and extracted exhaustively with $CHCl_3$. The chloroform residue, remaining after evaporation of the washed ($H_2O$) and dried ($K_2CO_3$) extract, was crystallized from methanol–ether and recrystallized from ether to give rosettes of compound **11** (3.1 g): mp 117–118°; uv max 284 mμ (log ε 3.48), 299 (3.53); ir 3400 $cm^{-1}$ (NH).

*Anal.* Calcd for $C_{28}H_{34}N_2O_5$: C, 70.27; H, 7.16; N, 5.85. Found: C, 70.17; H, 7.15; N, 5.91.

**1,2,3,10-Tetramethoxy-9-hydroxyaporphine (Racemic 4).**—The diamine **11** (956 mg) was dissolved at 5° in a solution of 20 ml of glacial HOAc, 20 ml of $H_2O$, and 2 ml of concentrated $H_2SO_4$. A solution of $NaNO_2$ (152 mg) in 5 ml of $H_2O$ was added dropwise. After 15 min of stirring the green diazonium salt solution was added dropwise while cold into 100 ml of a boiling 25% (v/v) $H_2SO_4$ solution. The resulting red solution was treated with 3 g of activated zinc and refluxed 1 hr, then diluted with water, filtered, cooled in ice, made basic with $NH_4OH$, and then extracted with $CHCl_3$. The extract after drying ($K_2CO_3$) yielded on evaporation a dark oil which was chromatographed on 30 g of silicic acid (Mallinckrodt) starting with $CHCl_3$ as eluting solvent. The chloroform–methanol (99:1) effluent residue crystallized from $CH_3OH$ as cubes (190 mg) of racemic aporphine **4**: mp 206–207°; uv max 312, 301, 231 mμ (log ε 4.08, 4.13, 4.15); in 0.01 *N* methanolic KOH, uv max 323 mμ (log ε 4.28); nmr δ 2.53 ($NCH_3$), 3.73 ($OCH_3$), 3.90 (2 $OCH_3$), 3.97 ($OCH_3$), 5.5 (broad OH, lost in $D_2O$), 6.84 (s, $H_8$) and 7.96 (s, $H_{11}$). The compound gave a positive $FeCl_3$ test.

*Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.08; H, 6.88; N, 3.89.

(15) Z. F. Ismailov, M. V. Telezhenetskaya, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, **4**, 136 (1968); Kh. S. Umarov, M. V. Tetezhenetskaya, Z. F. Ismailov, and S. Yu. Yunusov, *ibid.*, **3**, 353 (1967).

(16) Analyses were performed by Dr. Alfred Bernhardt, West Germany. Melting points are uncorrected. Nmr spectra were run in $CDCl_3$ (tetramethylsilane as internal standard) unless stated otherwise, using a Varian A-60 instrument; ultraviolet spectra were taken in $CH_3OH$ on a Cary Model 15 spectrophotometer; infrared spectra were taken in $CHCl_3$ or in KBr windows on a Perkin-Elmer Model 237 or 257 instrument; and ORD, CD curves, and optical rotations were measured in methanol on a Jasco Model ORD/UV-5 spectropolarimeter with a CD attachment.

**Resolution of 1,2,3,10-Tetramethoxy-9-hydroxyaporphine to the (+)-(*S*) Enantiomer 4.**—The aporphine (racemic **4**, 700 mg) and di-*p*-toluoyl-(−)-tartaric acid (716 mg) were dissolved in 20 ml of EtOH by slight warming. After standing overnight the crude crystalline di-*p*-toluoyl (−)-tartarate [diastereoisomer with (−)-(*R*) enantiomer] was collected by filtration as was a second crop which formed on concentrating the filtrate by one-half. The base liberated from the mother liquor [the (+)-(*S*) enantiomer predominating] was mixed with an equal amount of di-*p*-toluoyl-(+)-tartaric acid and dissolved in the minimum amount of EtOH with warming. The long fibrous needles that formed overnight at room temperature were collected, washed with ether, and recrystallized from EtOH to give flat needles, mp 150–151°. The liberated free base was subjected twice more to the whole operation and finally crystallized from $CH_3OH$ as cubes (180 mg) of (+)-(*S*)-1,2,3,10-tetramethoxy-9-hydroxyaporphine (**4**), mp 186–187°, $[\alpha]_D$ +108° (*c* 0.17, $CH_3OH$). Additional treatment with the resolving reagent did not affect the specific rotation.[17]

**Adiantifoline (1).**—A mixture of the (+)-(*S*)-aporphine **4** (350 mg), (+)-(*S*)-6′-bromolaudanosine (250 mg), anhydrous $K_2CO_3$ (250 mg), CuO (45 mg), KI (5 mg), and pyridine (5 ml) was heated with stirring, under nitrogen, in an oil bath at 138–144° for 9 hr. The cooled reaction mixture was dissolved in 25 ml of $CHCl_3$ and filtered and the filtrate was evaporated to dryness at reduced pressure. The residue was taken up in 10% HCl and washed with ether and the acid phase was basified with $NH_4OH$ and then extracted with ether. The ether solution was washed with 5% NaOH and water, then dried ($K_2CO_3$), and evaporated to leave a 370 mg of oily residue. Chromatography of the oil on 40 g of silicic acid was started beginning with $CHCl_3$ as eluent. The chlorform–methanol (98:2) eluent gave 40 mg (+)-6′-(*S*)-bromolaudanosine, and adiantifoline mixed in some runs with a trace of (+)-laudanosine was obtained with chloroform–methanol (96:4) as eluent. Removal of this contaminant was by thick layer (0.5 mm) chromatography on silica gel G (Merck) plates (20 cm × 20 cm) with benzene–acetone–diethylamine (32:32:1) as solvent. The adiantifoline band was located at $R_f$ 0.46. Extraction of the band, twice with boiling $CH_3OH$, left a residue, after evaporation of the solution, that was suspended in $CHCl_3$ and filtered. The filtrate residue crystallized from ethanol–ether to give adiantifoline as fine needles (67 mg, second crop 20 mg; 21% overall based on **12**), mp 142–143°, mmp 142–143° with natural adiantifoline.[18] The uv, ir, and nmr spectra and the CD curves were identical for the two samples.

***N*-(2,3,4-Trimethoxyphenylethyl)-3′-benzyloxy-4′-methoxy-6′-nitrophenylacetamide (9).**—To a stirred solution at 60° of 3-benzyloxy-4-methoxy-6-nitro-ω-diazoacetophenone[12] (6.6 g) in 200 ml of dry benzene containing 0.66 g of freshly prepared $Ag_2O$ was added a solution of 2,3,4-trimethoxyphenylethylamine[7] (liberated from 4.95 g of the HCl salt) in 120 ml of dry benzene. After 3 hr, an additional 0.66 g of $Ag_2O$ was added and the reaction mixture was refluxed for 0.5 hr. The mixture was filtered through diatomaceous earth and the insolubles were washed with benzene. The combined filtrate and washings (500 ml) on concentrating deposited 7.83 g of buff-colored crystals. Recrystallization from EtOH furnished compound **9** as fibrous needles: mp 170–171°; ir 3375 (NH) and 1660 $cm^{-1}$ (amide C=O).

*Anal.* Calcd for $C_{27}H_{30}N_2O_8$: C, 63.52; H, 5.92. Found: C, 63.39; H, 5.74.

**1-(3′-Benzyloxy-4′-methoxy-6′-nitrobenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (10).**—The amide **9** (2.65 g), 10 ml of $CHCl_3$, and 20 g of polyphosphoric ester[14] were stirred at room temperature under anhydrous conditions for 48 hr. The green reaction mixture was then poured into 200 ml of 5% HCl and nitrogen was bubbled through the stirred solution while the chloroform was evaporated. The filtered solution was basified with $NH_4OH$ and extracted with ether. The dried ($Na_2SO_4$) ether solution on evaporation left a heavy oil that crystallized from methanol to give 1.2 g of the imine **10**, mp 179–181°.

*Anal.* Calcd for $C_{27}H_{28}N_2O_7$: C, 65.84; H, 5.73; N, 5.69. Found: C, 65.72; H, 5.72; N, 5.75.

(+)-(*S*)-**1,2,3,9,10-Pentamethoxyaporphine (Thalicsimidine) (13).**—The aporphine **4** (100 mg) dissolved in methanol was mixed with an ethereal solution of diazomethane (300 mg) and the mixture was kept overnight in the refrigerator. After evaporation of the solvent, the residue was first crystallized from EtOH to give pale yellow needles and then from hexane to furnish colorless needles of **13** (89 mg): mp 134–135°; $[\alpha]_D$ +66° (*c* 2.02, $CH_3OH$); uv max 224, 282 and 302 mμ (log ε 4.48, 4.17, and 4.14); nmr[19] δ 2.55 (s, 3 H, $NCH_3$) 3.75 (s, 3 H, $OCH_3$), 3.91 (s, 3 H, $OCH_3$), 3.94 (s, 6 H, $OCH_3$), 3.98 (s, 3 H, $OCH_3$), 6.81 (s, 1 H, Ar H) and 8.00 (s, 1 H, Ar H); picrate mp 141° dec [lit.[15] mp 131–132°; $[\alpha]_D$ +57.85° (*c*, 0.96 EtOH); uv max 220, 280, and 300 mμ; nmr δ 2.47 (s, 3 H, $NCH_3$), 3.64 (s, 3 H, $OCH_3$), 3.82 (s, 3 H, $OCH_3$), 3.85 (s, 6 H, $OCH_3$), 3.88 (s, 3 H, $OCH_3$), 6.70 (s, 1 H, Ar H), 7.89 (s, 1 H, Ar H); picrate mp 141–150°].

*Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.49; H, 7.13; N, 3.80.

**1-(3′-Hydroxy-4′-methoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (14).**—Compound **6** (500 mg) was heated on the steam bath for 1.5 hr in a solution of 12.5 ml of acetic acid and 12.5 ml of 20% HCl. The reaction solution was diluted with ice, basified with $NH_4OH$, and extracted with ether. The ether residue crystallized from absolute ethanol–ether as white microcrystals (220 mg) of **14**: mp 121–122°; uv max 282 mμ (log ε 3.89); nmr δ 2.6–3.3 (envelope 6 H, methylene protons), 3.82 (s, 6 H, $OCH_3$), 3.88 (s, 6 H, $OCH_3$), 4.10 (m, 1 H, methine), 6.51 (s, 1 H, $H_8$), 6.77 (m, 3 H, $H_2'$, $H_5'$, $H_6'$), and a $D_2O$ exchangeable peak at 4.30 (2 H).

*Anal.* Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.78; H, 6.97; N, 3.77.

**1-(3′,4′-Dimethoxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (16).**—To a solution of 15 mg of compound **14** in 3 ml of $CH_3OH$ was added an ethereal solution of diazomethane (~0.1 g). After the mixture was allowed to stand overnight in the cold, the solvent was removed and the resulting residue which would not crystallize was passed through a column of alumina (1 g). The benzene effluent (15 ml) yielded a homogeneous glass (11 mg) which formed a crystalline hydrochloride (from methanol–ether) of compound **16**: mp 210–212°; nmr ($CD_3OD$) δ 3.86 (s, 9 H, $OCH_3$), 3.91 (s, 3 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$), 6.86 (s, 3 H, Ar H), and 6.95 (s, 1 H, Ar H). Since the salt and base were not very stable, the acetate, mp 100–101°, was prepared for analysis.

*Anal.* Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.56; H, 7.07; N, 3.52.

**1-(3′-Hydroxy-4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (15).**—Compound **7** hydrochloride (500 mg) in 12.5 ml of glacial acetic acid and 12.5 ml of 20% HCl was heated on the steam bath for 1.5 hr. The reaction mixture was diluted with ice, basified with $NH_4OH$, and extracted with ether. The ether residue crystallized from ether to give 160 mg of **15**: mp 110–111°; uv max 282 mμ (log ε 3.76); nmr δ 2.51 (s, 3 H, $NCH_3$), 2.6–3.4 (envelope, 6 H, $CH_2$ protons), 3.58 (s, 3 H, $OCH_3$ at $C_5$), 3.83, 3.85, 3.87 (s, 3 H each, $OCH_3$ at $C_5$, $C_6$, and $C_4'$), ~3.7 (m, 1 H, methine), 5.6 (broad, 1 H, OH, $D_2O$ exchangeable), 5.97 (s, 1 H, $H_8$), and 6.4–6.9 (m, 3 H, $H_2'$, $H_5'$, and $H_6'$).

*Anal.* Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.42; H, 7.35; N, 3.75.

**1-(3′,4′-Dimethoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (17).**—The phenol **15** (50 mg) was dissolved in methanol and treated with an ethereal solution of diazomethane prepared from 1.07 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. The next day the solution was filtered to remove a slight precipitate and evaporated to dryness. The nonphenolic residue yielded the hydrochloride of **17** (40 mg) from methanol–ether: mp 169–170°; uv max 282, 218 mμ (log ε 3.60, 4.12); nmr (free base) δ 2.53 (s, 3 H, $NCH_3$), 2.5–3.1 (envelope, 6 H, $CH_2$ protons), 3.59 (s, 3 H, $OCH_3$ at $C_7$), 3.79 (s, 3 H, $OCH_3$), 3.85 (s, 9 H, 3 $OCH_3$), ~3.7 (m, 1 H, methine), 5.97 (s, 1 H, $H_8$) and 6.4–6.9 (m, 3 H, $H_2'$, $H_5'$, $H_6'$).

*Anal.* Calcd for $C_{22}H_{29}NO_5 \cdot HCl$: C, 62.33; H, 7.14; N, 3.31. Found: C, 62.04; H, 7.21; N, 3.40.

(17) The extent of resolution was also checked by circular dichroism. The maximum values approached were $[\theta]_{312}$ −17,400, $[\theta]_{300}$ −22,000, $[\theta]_{278}$ −26,700, and $[\theta]_{242}$ +225,000.

(18) Adiantifoline as reported in ref 4 is polymorphic. The synthetic product from hexane gave a microcrystalline powder, mp 107–108°. The natural product also furnishes the same low melting solid when crystallized from the same solvent.

(19) All of the peak values differ by δ +0.10 ± 0.01 units from those in the literature. Such a uniform displacement was considered to be due to a variable in the determination of the spectrum and not to signify a compound difference.

**Registry No.**—**1**, 20823-96-5; (±)-**4**, 24314-85-0; (+)-(*S*)-**4**, 24314-86-1; **5**, 24214-36-6; **6** HCl, 29883-53-2; **7** HCl, 29883-54-3; **8** HCl, 29883-55-4; **9**, 29969-76-4; **10**, 29969-77-5; **11**, 29883-56-5; **13**, 19775-47-4; **14**, 29883-57-6; **15**, 29883-58-7; **16**, 29969-78-6; **16** HCl, 29883-59-8; **17** HCl, 29883-60-1.

# Photochemical Synthesis of Aporphines[1]

S. MORRIS KUPCHAN,*[2] JERRY L. MONIOT, RAMESH M. KANOJIA, AND JOHN B. O'BRIEN

*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, and Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706*

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The photolysis of iodo aromatic compounds has been employed as the key step in new synthetic routes to aporphines. Photocyclization of 1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochlorides (**18**, **19**, **10**, **11**) yielded noraporphines **29** and **30** and aporphines **33** and **34** directly. Photocyclization of *N*-acyl-1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinolines (**14**–**17**) followed by hydrolysis gave noraporphines **25**–**28**. Photolysis of urethanes **12** and **13** afforded substituted dehydronoraporphines **23** and **24**, and two-step reduction gave (±)-aporphine (**33**) and (±)-nuciferine (**34**). Photolysis of *N*-carbophenoxy-1-(2′-iodobenzyl)-1,2,3,4-tetrahydroisoquinolines **20** and **21** followed by one-step reduction afforded good yields of (±)-aporphine (**33**) and (±)-nuciferine (**34**). The routes *via* photocyclization of *N*-acyl iodo aromatic compounds have yielded oxygenated aporphines and noraporphines in the best yields reported to date.

Aporphines, which contain the tetracyclic ring system shown in structure **33**, have been the subject of considerable chemical and pharmacological interest for many years.[3] Nevertheless, all aporphines synthesized up to 1966 were obtained only from the corresponding 1-(2′-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines by way of a Pschorr-type cyclization, usually in quite low yield.[4] In 1966, two mechanistically different photochemical syntheses of aporphines were reported, one involving an oxidative stilbene–phenanthrene photocyclization,[5,6] and the other involving photocyclization of iodostilbenes to phenanthrenes.[1a,7] The present paper gives details of the photocyclization of iodobenzyltetrahydroisoquinolines to noraporphines and aporphines and an improved method for the synthesis of *N*-acyl and *N*-carbamyl noraporphines and aporphines. In addition, we now report a novel modification of the syntheses in which iodobenzylidene tetrahydroisoquinolines are cyclized to substituted dehydronoraporphines. Since the dehydronoraporphines can be readily reduced to aporphines, this method constitutes an efficient aporphine synthesis.[8]

## Results

The photolysis of 1-(2′-iodobenzyl)tetrahydroisoquinolines was investigated as the most direct route to the aporphine ring system. Condensation of the appropriately substituted β-phenethylamines **1** and **2** with *o*-iodophenylacetyl chloride (**3**) gave the amides **4** and **5** (Sheme I). Bischler–Napieralski cyclization of **4** and **5** using polyphosphate ester[9] gave the 3,4-dihydroisoquinolines **6** and **7** in 93–98% yields. Direct reduction with sodium borohydride afforded the noraporphine precursors **18** and **19**, respectively. Treatment of **6** and **7** with methyl iodide followed by reduction of the stable quaternary iodides **8** and **9** with sodium borohydride gave the aporphine precursors **10** and **11**, respectively. Photolysis of **18** gave a complex intractable mixture of products which showed negligible uv absorption in the region characteristic of aporphines (270 mμ). Apparently, the presence of the free electron pair on nitrogen was detrimental to the desired photocyclization of **18**, and other reactions predominated. Salt formation was conceived as a potential method to circumvent this effect. Photolyses of the hydrochloride salts of **18**, **19**, **10**, and **11** were carried out in methanol–water mixtures in the presence of sodium bisulfite and afforded the desired noraporphines (**29** and **30**) and aporphines (**33** and **34**) in 13–20% yields (Table I). The low yield of aporphine **33** was found to be attributable to formation during the reaction of a secondary product which had the spectral characteristics of a phenanthrene. The *N*-methyl derivative of this product was shown to be identical with **22**, prepared by Hofmann degradation of aporphine **33**. This product is presumed to have resulted from cleavage of the initially formed aporphine in a manner analogous to the Hofmann reaction.

To avoid this side reaction, the photolysis of the less labile *N*-acyl precursors was investigated, with a view toward subsequent hydrolysis of the cyclization products to noraporphines. The noraporphine precursors **18** and **19** were treated with acetic anhydride–pyridine to obtain the acetamides **14** and **15** and with benzoyl chloride–pyridine to obtain the benzamides **16** and **17**, respectively. Photolysis of the *N*-acyl precursors **14**, **15**, **16**, and **17** in benzene solution in the presence of sodium thiosulfate afforded the substituted noraporphines

(1) (a) A portion of this work was reported in a preliminary communication: S. M. Kupchan and R. M. Kanojia, *Tetrahedron Lett.*, 5353 (1966). (b) This work was supported by grants from the National Institutes of Health (HE-13184 and CA-12059).

(2) Department of Chemistry, University of Virginia.

(3) For recent reviews of aporphine alkaloids, see (a) M. Shamma, *Alkaloids*, **9**, 1 (1967); (b) M. P. Cava and A. Venkateswarlu, *Annu. Rep. Med. Chem.*, 331 (1968).

(4) For a brief review of the synthesis of aporphines up to 1960, see A. R. Pinder in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1960, Chapter 25.

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(8) After completion of this work, the nonoxidative photocyclization of chloro- and bromostilbene noraporphine precursors was reported: M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *ibid.*, **35**, 175 (1970). The authors proposed, however, that their photocyclizations proceeded principally *via* closure to dihydrophenanthrene intermediates rather than by photochemical homolysis of the aryl halide bond involved in the photocyclization of iodostilbenes[7] [*cf.* R. K. Sharma and N. Kharasch, *Angew. Chem. Int. Ed. Engl.*, **7**, 36 (1968)].

(9) Y. Kamaoka, E. Sato, O. Yonematsu, and Y. Ban, *Tetrahedron Lett.*, 2419 (1964).