talline material with nmr δ 1.19 (s, 3α-methyl) and 0.78 (s, 4aβ-methyl). The minor epimeric product could not be detected.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.04; H, 10.30.

B.—A solution of 0.10 g (0.49 mmol) of the β-keto nitrile **18** and 0.10 g (2.6 mmol) of sodium borohydride in 10 ml of ethanol was stored at 22° for 20 hr, poured into water, made basic with sodium hydroxide and then acidic with hydrochloric acid, and extracted with dichloromethane. Concentration and distillation at 90–110° (0.3 mm) gave 87 mg of material, lacking ir carbonyl absorption and consisting of a small amount of oil and predominantly of a crystalline product **26**, mp 133–134°; nmr δ 1.46 (s, 3α-methyl) and 1.17 (s, 4aβ-methyl). The reduction product was dissolved in 10 ml of dry benzene and 15 drops of dry triethylamine. A solution of 10 drops of methanesulfonyl chloride in 10 ml of dry benzene was added, under nitrogen, during 30 min. After 9 hr the mixture was poured into water and extracted with dichloromethane, and the extracts were washed with dilute hydrochloric acid and sodium bicarbonate solution. Concentration under vacuum gave a mesylate with nmr δ 3.12 (s, mesylate methyl), 1.49 (s, 3α-methyl), and 1.18 (s, 4aβ-methyl). A solution of the mesylate in 5 ml of dry dimethylformamide, 50 mg of lithium carbonate, and 50 mg of lithium chloride was heated at 210–220° for 4 hr in a sealed tube. The reaction mixture was poured into water and extracted with ether, and the extracts were concentrated and distilled to a maximum of 120° (0.3 mm). The nmr showed δ 5.56 (olefinic protons), 1.45 and 1.08 (s, 3α- and 4aβ-methyl in **20**), and 1.52 and 1.18 [s, 3α- and 4aβ-methyl in **28** (minor component)]. The distillate, taken up in 5 ml of petroleum ether, gave 15 mg of the chloronitrile **28**, mp 164–165°, which sublimed at 120° (0.3 mm).

Anal. Calcd for $C_{18}H_{20}NCl$: C, 69.14; H, 8.93; N. 6.21. Found: C, 69.36; H, 9.06; N, 6.17.

The petroleum ether soluble portion, redistilled at 90° (0.3 mm), gave 57 mg of olefinic nitrile **20**, which was hydrogenated in 5 ml of ethanol with 50 mg of 10% palladium on charcoal during 4 hr. Filtration, addition of water, extraction with dichloromethane, concentration, and distillation at 90° (0.3 mm) gave 44 mg of the saturated nitrile **21**, mp *ca.* 30°, nmr δ 1.34 (s, 3α-methyl) and 1.15 (s, 4aβ-methyl). The nitrile **21** was hydrolyzed to the acid **24** by heating in a steel bomb with 2 g of potassium hydroxide and 10 ml of methanol for 20 hr at 170° and 24 hr at 210°. The reaction mixture was poured into water and extracted with ether, the ether was extracted with dilute sodium hydroxide, and the combined aqueous portions were acidified and extracted with dichloromethane. Concentration and distillation at 105° (0.001 mm) gave 34 mg of acid **24**, mp 81–83°. The nmr and ir spectra of this product were identical with those of the sample obtained from the ester **31**. Vpc on an SE 30 column at 240 and 200° showed identical retention times of the samples.

C.—Clemmensen reduction of 66 mg of the β-keto nitrile **18**, according to the procedure described for the β-keto ester **31**, gave 40 mg of an olefinic nitrile with the expected methyl singlets at δ 1.45 and 1.08 for **20** as well as major singlets at δ 1.62 and 1.03 ascribed to the isomeric olefin **22** and minor singlets for the dihydro compound **21** at δ 1.34 and 1.15. Catalytic reduction, as described above, gave primarily the nitrile **21** with δ 1.34 and 1.15 singlets and the *cis*-decalin **23** with δ 1.30 and 0.96 as minor singlets. Hydrolysis gave a mixture of decalin acids with nmr δ 1.19 and 0.78 methyl singlets for **24** and δ 1.57 and 1.01 for **25**.

Registry No.—**4**, 22252-96-6; **5**, 22252-97-7; **6**, 22249-29-2; **7**, 22249-30-5; **8**, 22249-31-6; **9**, 22249-32-7; **10**, 22249-33-8; **11**, 22249-34-9; **12**, 22256-09-3; **15**, 22256-10-6; **16**, 22256-11-7; **17**, 22256-12-8; **18**, 22256-13-9; **24**, 22256-14-0; **26**, 22256-15-1; **28**, 22256-16-2; **30**, 22256-17-3.

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Photochemical Routes to Aporphines. New Syntheses of Nuciferine and Glaucine[1]

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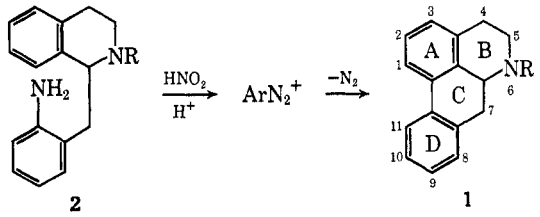
The stilbene–phenanthrene photocyclization reaction has been employed as the key step in new synthetic routes to the aporphine alkaloids nuciferine (**4**) and glaucine (**3**). Thus, oxidative irradiation of 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**6**) or 1-veratrylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**8**) yields, respectively, N-carbethoxy-6a,7-dehydronornuciferine (**13**) or N-carbethoxy-6a,7-dehydronorglaucine (**14**). An efficient two-step reduction procedure is described for the conversion of the photolysis products **13** and **14** into nuciferine and glaucine. A cleaner variation of this aporphine synthesis consists in the *nonoxidative* formation of urethans **13** and **14** by the irradiation of the 2′-chloro derivative (**7**) of **6** and the 6′-bromo derivative (**9**) of **8**, respectively. The latter transformations represent the first examples of photochemical syntheses of phenanthrenes by the loss of hydrogen chloride or hydrogen bromide from a simple stilbene system.

The aporphines comprise a group of about 90 alkaloids, all of which contain the tetracyclic ring system shown in structure **1**.[3] Despite continuing interest in both the chemistry and pharmacology of these compounds, all aporphines synthesized up to 1966 were obtained only from the corresponding 1-(2′-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines (*e.g.*, **2**) by way



2 **1**

of a Pschorr-type cyclization, sometimes in quite low yield.[4] Gadamer's synthesis of glaucine (**3**) in 1911 was the first successful application of the reaction.[5]

(1) A portion of this work (the synthesis of **4** from **6**) was reported as a preliminary communication: M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966).

(2) To whom all inquiries should be addressed: Department of Chemistry, University of Pennsylvania, Philadelphia, Pa. 19104.

(3) For recent reviews of the aporphine alkaloids, see (a) M. Shamma in "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 1; (b) M. P. Cava and A. Venkateswarlu, *Ann. 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 Publishing Co., New York, N. Y., 1960, Chapter 25.

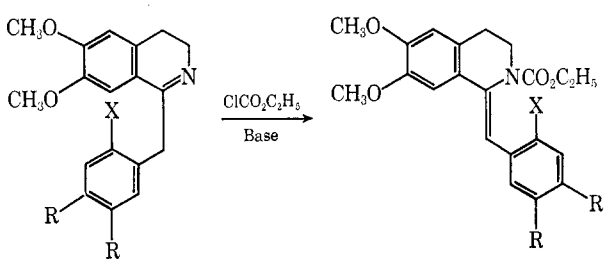
(5) J. Gadamer, *Arch. Pharm.* (Weinheim), **249**, 680 (1911).

In 1966, we reported briefly the discovery of a fundamentally new synthetic route to aporphines, illustrated by a new synthesis of nuciferine (**4**); the key step in this synthesis involved the application of the well-known oxidative stilbene–phenanthrene photocyclization reaction to effect the formation of ring C of the aporphine system.[6,7] The present paper gives details of an improved version of this synthesis and of a similar synthesis of glaucine (**3**). In addition, we now report a novel modification of the nuciferine and glaucine syntheses in which the key step involves a nonoxidative photocyclization of a halogenated stilbene-type precursor.[8]

Results

Synthesis and Photocyclization of 1-Benzylidene-2-carbethoxy-1,2,3,4-tetrahydroisoquinolines.—N-Acyl derivatives of 1-benzylidene-1,2,3,4-tetrahydroisoquinolines were chosen as suitable starting material for photocyclization studies. Compounds of this general type are readily available by the action of acylating agents on 1-benzyl-3,4-dihydroisoquinolines.[9] The N-carbethoxy group was employed in the work described here, since it can be converted in due course into an N-methyl group. Thus, the reaction of ethyl chloroformate with 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**5**)[10] under Schotten–Baumann conditions gave 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**6**) in 73% yield. The nmr spectrum of ester **6** showed a triplet at δ 0.78, indicating considerable shielding of the methyl of the carbethoxy group by the benzylidene phenyl; ester **6** was thus shown to be the stereoisomer having the *trans* configuration of the two aromatic substituents about the double bond.

The analogous esters **7**, **8**, and **9** were prepared by the same procedure, starting from ethyl chloroformate and the dihydroisoquinolines **10**,[11] **11**,[12] and **12**, respectively. Esters **7**, **8**, and **9** were assigned the same *trans* stereochemistry as ester **6**, since they all showed a methyl triplet centered in the region of δ 0.87–0.80.



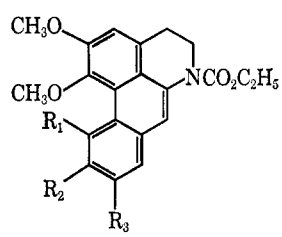
5, X = R = H
10, X = Cl; R = H
11, X = H; R = OCH_3
12, X = Br; R = OCH_3

6, X = R = H
7, X = Cl; R = H
8, X = H; R = OCH_3
9, X = Br; R = OCH_3

The irradiation of ester **6** was carried out in ethanol solution under nitrogen, using iodine as an oxidant, to give N-carbethoxy-6a,7-dehydronornuciferine (**13**), after extensive purification. The best yield of **13** (35%) was obtained in the presence of cupric acetate, a reagent previously shown to have a favorable effect on the yield of phenanthrene obtained in the oxidative photocyclization of a simple dimethoxystilbene.[13] The nmr spectrum of **13** was fully consistent with the assigned structure and showed as significant features an unshielded carbethoxy methyl (triplet at δ 1.31) and the anticipated low-field proton at C-11 (unresolved multiplet at δ 9.58) of the aporphine system.

A similar irradiation of ester **8** in ethanol solution in the presence of iodine and cupric acetate afforded, in 19% yield, N-carbethoxy-6a,7-dehydronorglaucine (**14**). In theory, photocyclization of **8** could lead not only to **14** but also to N-carbethoxy-6a,7-dehydrocatalpifoline (**15**). We were unable, however, to isolate any such product from the photolysis mixture. The nmr spectrum of **14** showed the expected features, including the unshielded carbethoxy methyl (triplet at δ 1.32) and the low-field C-11 proton as a sharp singlet at δ 9.16.

The chloro ester **7** and the bromo ester **9** were best photolyzed under nitrogen in methanol solution in the presence of calcium carbonate as an acid scavenger but in the absence of any added oxidant. Under these conditions, hydrogen halide was eliminated smoothly to give the dehydroaporphine derivatives **13** and **14** in yields of 32 and 24%, respectively. From the point of view of product isolation, the halo ester photolyses were much cleaner and the products were much more readily isolated than in the case of the oxidative photocyclizations. One reason for this is that the nonoxidative cyclizations proceeded essentially to completion, obviating the need for an otherwise difficult separation of starting material and cyclized product.



13, $R_1 = R_2 = R_3 = H$
14, $R_1 = H$; $R_2 = R_3 = OCH_3$
15, $R_1 = R_2 = OCH_3$; $R_3 = H$

Conversion of the Photocyclization Products into Aporphines.—The conversion of esters **13** and **14** into the alkaloids nuciferine (**4**) and glaucine (**3**) involves the reduction of both the 6a,7 double bond and the N-carbethoxy group of each ester. Esters **13** and **14** proved to be very resistant to catalytic reduction, so that reduction of the 6a,7 double bond as the first step was impractical. Lithium aluminum hydride in ether reduced **13** and **14** slowly to give dehydronuciferine (**16**) and dehydroglaucine (**17**), respectively, but the products were purified only with great difficulty, probably because of incomplete reduction of the ester group, leading to dehydroaporphanes lacking the

(6) For some recent reviews of the stilbene–phenanthrene photocyclization, see (a) F. R. Stermitz in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 247; (b) M. Scholz, F. Dietz, and M. Muhlstadt, *Z. Chem.*, **7**, 329 (1967).

(7) (a) This synthetic method was discovered and reported simultaneously by another research group: N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966). These workers prepared several dehydroaporphanes (including the urethan **14**), but did not report the synthesis of any natural aporphine alkaloid. (b) For a mechanistically different photochemical aporphine synthesis proceeding *via* an *o*-iodobenzyltetrahydroisoquinoline, see S. M. Kupchan and R. M. Kanojia, *ibid.*, 5353 (1966).

(8) For the first report of the photochemical loss of HCl from a stilbene-like system (actually a complex xanthylium salt), see W. Dilthey and F. Quint, *Chem. Ber.*, **69**, 1575 (1936).

(9) M. Hamon, *Ann. Chim.*, [13] **10**, 213 (1965).

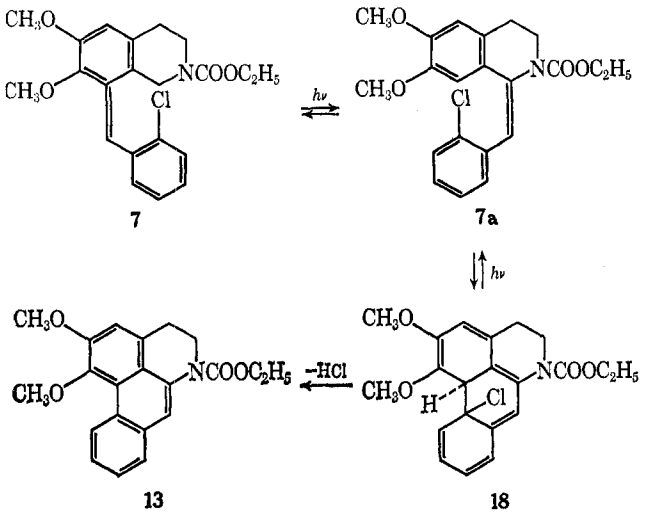
(10) G. Tsatsas, *Ann. Pharm. Fr.*, **10**, 61 (1952).

(11) C. Viel, R. Dorme, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1956 (1966).

(12) A. Pictet and M. Finkelstein, *Ber.*, **42**, 1979 (1909).

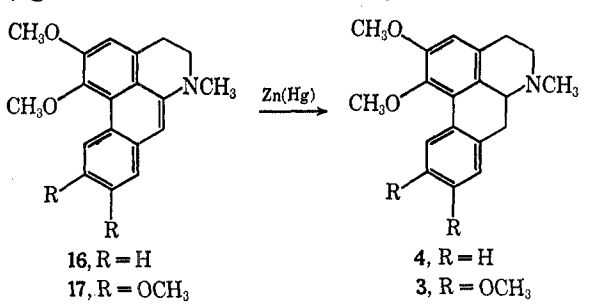
(13) D. J. Collins and J. J. Hobbs, *Chem. Ind.* (London), 1725 (1965).

SCHEME I
MECHANISM A



N-methyl function. This type of side reaction has been reported by others in the lithium aluminum hydride reduction of a closely related ester.[7a] By-product formation was eliminated by carrying out the hydride reduction in the presence of aluminum chloride; this readily afforded the dehydro bases **16** and **17** in over 70% yield. Since the time when this work was carried out, dehydroglaucine (**17**) has been reported as a naturally occurring alkaloid.[14] The reported melting point (133–134°) of the natural base is at variance with the melting point (115–116°) of the carefully purified synthetic base, suggesting the existence of allotropic forms of this compound.

Catalytic reduction of the 6a,7 double bond of **16** and **17** could be achieved,[1] but the reaction was sluggish even when Adams catalyst in acetic acid was employed. The desired reduction was achieved chemically in a convenient manner using amalgamated zinc in aqueous ethanolic hydrochloric acid, leading to good yields of (±)-nuciferine (**4**) and (±)-glaucine (**3**). Whereas natural (+)-glaucine is highly crystalline, our (±)-glaucine was amorphous but it was readily converted into the crystalline picrate. The amorphous nature of (±)-glaucine has also been noted by others.[15]

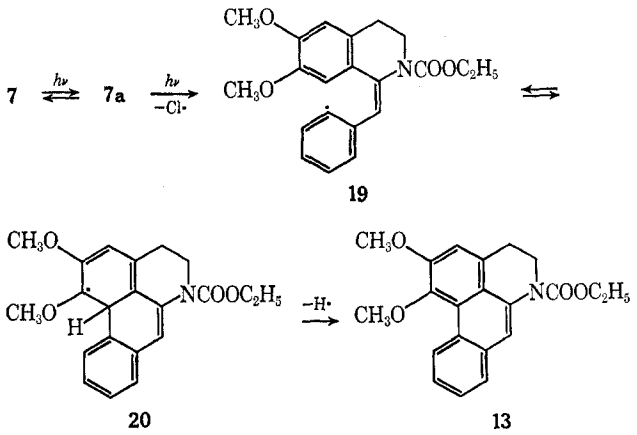


Discussion

In addition to the practical synthetic value of this study, the nonoxidative photocyclization of the chloro stilbene **7** and the bromo stilbene **9** poses an interesting mechanistic question. Two quite different mechanisms can be written for these reactions, as illustrated for the chloro compound **7** in Schemes I and II.

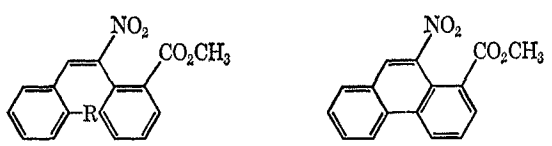
(14) H. G. Kiryakov, *Chem. Ind.* (London), 1807 (1968).
(15) A. H. Jackson and J. A. Martin, *J. Chem. Soc., C*, 2061 (1966).

SCHEME II
MECHANISM B



In mechanism A, the primary photochemical conversion of the *trans* chloro stilbene **7** to its *cis* isomer **7a** is followed by the reversible isomerization of the latter to the dihydrophenanthrene intermediate **18**; irreversible loss of hydrogen chloride from **18** yields the observed phenanthrene **13**. In mechanism B, formation of the *cis* chloro stilbene **7a** is followed by photochemical homolysis of the carbon–halogen bond to give the *cis* radical **19**; ring closure of the latter yields the tetracyclic radical (**20**) and leads to the observed phenanthrene (**13**) by loss of a hydrogen atom.

Kupchan and Wormser have reported the photolytic conversion of a number of *o*-iodo stilbenes to the corresponding phenanthrenes in high yield and have presented evidence against the intermediacy of a dihydrophenanthrene in this process. Specifically, photolysis of 2-carbomethoxy-2′-iodo-α-nitro-*cis*-stilbene (**21**) affords methyl 10-nitro-1-phenanthroate (**22**), whereas the corresponding chloro stilbene **23** fails to cyclize photochemically.[16] It has also been observed, however, that the unhalogenated nitro stilbene **24** is not con-



verted to phenanthrene **22** under oxidative photochemical conditions;[16] inhibition of the oxidative stilbene–phenanthrene reaction by a nitro substituent has been noted in other instances.[17] It seems reasonable to conclude, therefore, that neither the iodo stilbene **21** nor the chloro stilbene **23** can cyclize to a dihydrophenanthrene intermediate because of the presence of the nitro group in the molecule. Cyclization of **21** is successful, nevertheless, because of the ready photochemical homolysis of the weak carbon–iodine bond. In general, aryl iodides are known to be easily cleaved photochemically, whereas the corresponding aryl chlorides are far more stable under the same conditions.[18]

(16) S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).
(17) F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964), and earlier references cited therein.
(18) R. K. Sharma and N. Kharasch, *Angew. Chem. Intern. Ed. Engl.*, **7**, 36 (1968).

The ready photochemical dehydrohalogenation of chloro stilbene **7**, in contrast to the reported stability of the nitro chloro stilbene (**23**), suggests strongly that mechanism A is involved in the conversion of **7** to phenanthrene **13**. By analogy, the conversion of bromo stilbene **9** to phenanthrene **14** probably proceeds also by mechanism A; mechanism B may be at least partially operative in this case, however, in view of the greater ease of photochemical cleavage of the carbon–bromine bond in aryl bromides.[18]

Experimental Section

Melting points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Uv spectra were determined on ethanol solutions with a Perkin-Elmer Model 202 spectrophotometer. Nmr spectra were recorded for deuteriochloroform solutions with a Varian A60A nmr spectrometer.

(±)-**Nuciferine** *via* **the Oxidative Route. A. 1-Benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (6).**—A solution of 6.36 g (20 mmol) of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**5**) hydrochloride[10] in 50 ml of water was treated with 50 ml of a warm 20% aqueous solution of sodium carbonate. The resulting suspension was cooled to 5–10° and was mixed with a solution of 5.0 g (46 mmol) of ethyl chloroformate in 50 ml of chloroform. After being stirred for 0.5 hr at 5–10°, the reaction mixture was separated and the organic layer was washed with 1 *N* hydrochloric acid and water and dried over magnesium sulfate. Evaporation *in vacuo* gave a crystalline solid which was recrystallized from absolute ethanol to give 5.16 g (73%) of the product (**6**), mp 133–134°.

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.54; H, 6.41; N, 3.74.

B. N-Carbethoxy-6a,7-dehydronornuciferine (13).—A well-stirred solution of 0.353 g (1.0 mmol) of 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**6**), 0.102 g (4.02 mmol) of iodine, and 0.200 g (1.0 mmol) of cupric acetate dihydrate in 200 ml of ethanol was irradiated under nitrogen at room temperature for 15 hr (Hanovia 450-W medium-pressure lamp, housed in a water-cooled quartz insert; the irradiation was interrupted at 3-hr intervals to remove a dark-colored polymeric precipitate from the surface of the insert). The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with chloroform. The chloroform extract was concentrated and chromatographed with chloroform on grade I neutral alumina. The early fractions gave 0.045 g of the product (**13**). Later fractions were combined, concentrated to a small volume, and subjected to preparative thin layer chromatography on silica gel with 1:2 ether–benzene to give an additional 0.079 g of product (total yield 35%): mp 128–130° (from methanol); λ_{max}^{EtOH} 256 (ε 39,000), 263 (ε 44,000), 311 (ε 11,500), 323 (ε 11,500), 356 (ε 1800), and 735 mμ (ε 1900).

Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.43; H, 5.94; N, 3.75.

C. Dehydronuciferine (16).—A solution of 0.0703 g (0.20 mmol) of N-carbethoxy-6a,7-dehydronuciferine (**13**) in 1.0 ml of dry tetrahydrofuran (THF) was mixed with 1.0 ml of a stock solution of lithium aluminum hydride and aluminum chloride in THF. [The stock solution contained 0.0228 g/ml (0.6 mmol/ml) of lithium aluminum hydride and 0.0400 g/ml (0.3 mmol/ml) of aluminum chloride.] The reaction mixture was warmed on a hot plate (50°) for 45 min and was then worked up with ice and chloroform in the usual way. Evaporation of the chloroform under a stream of nitrogen afforded an oil which was crystallized from ethanol to give 0.042 g (71.5%) of dehydronuciferine (**16**): mp 130–131°; λ_{max}^{EtOH} 253 (ε 93,000), 264 (ε 96,000), 293 (ε 18,000), and 327 mμ (ε 31,000).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.51; H, 6.60; N, 4.59.

D. (±)-Nuciferine (4).—Dehydronuciferine (0.0706 g, 0.20 mmol) was added to a well-stirred mixture of amalgamated zinc dust in dilute hydrochloric acid–ethanol at 50–60°. (The zinc–acid mixture was prepared by adding 0.500 g of zinc dust to 1.0 ml of 3% mercuric chloride solution, followed by 6 ml of 2 *N* hydrochloric acid and 1.0 ml of ethanol.) The reaction mixture was stirred at 50–60° for 20 min; 0.5 ml of concentrated hydrochloric acid was added and stirring was continued for an additional 20 min. The excess zinc dust was removed by filtration and the filtrate was worked up with ammonium hydroxide and chloroform in the usual way to give an oil which, on crystallization from hexane, afforded 0.064 g (86%) of (±)-nuciferine: mp 134.5–135.5° (lit.[19] mp 136–137°), identical in ir, uv, and R_f with an authentic sample of (−)-nuciferine.

(±)-**Nuciferine** *via* **the Dehydrohalogenation Route. A. 1-(2′-Chlorobenzylidene)-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7).**—A solution of 7.20 g (22.8 mmol) of 1-(2′-chlorobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (**10**)[11] in 75 ml of chloroform was cooled to 15–20° and was mixed with 75 ml of 10% aqueous sodium carbonate solution and an excess [5.0 g (46 mmol)] of ethyl chloroformate (the last was added in 1-ml portions during 30 min). The reaction mixture was stirred for an additional 45 min. The chloroform layer was separated, washed with dilute hydrochloric acid, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was recrystallized from 2:3 chloroform–ethanol to give 4.90 g (55.6%) of the product (**7**), mp 169–170°.

Anal. Calcd for $C_{21}H_{22}ClNO_4$: C, 65.03; H, 5.72; Cl, 9.14; N, 3.61. Found: C, 64.79; H, 5.60; Cl, 9.36; N, 3.58.

B. N-Carbethoxy-6a,7-dehydronornuciferine (13).—A well-stirred suspension of 0.400 g (1.03 mmol) of 1-(2′-chlorobenzylidene)-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**7**) and 0.5 g of calcium carbonate in 250 ml of anhydrous methanol was irradiated for 19 hr under nitrogen at room temperature (Hanovia 450-W medium-pressure lamp housed in a water-cooled quartz insert fitted with Vycor filter). The reaction mixture was evaporated to dryness, the residue was extracted with chloroform, and the extract was concentrated to a small volume and subjected to column chromatography with alcohol-free chloroform on silica gel (12 g of E. Merck silica gel, 0.05–0.2 mm, containing 10% added water). Four 25-ml fractions were collected. Thin layer chromatography on silica gel (E. Merck SHF_{254}) developed with 1:200 absolute ethanol–chloroform showed that almost all of the desired product was in the second fraction. This fraction was concentrated to a small volume and was rechromatographed with alcohol-free chloroform on a column of silica gel containing 5% added water. The second 25-ml fraction was evaporated *in vacuo* to give an oil which on crystallization from methanol gave, in two crops, 0.114 g (32%) of N-carbethoxy-6a,7-dehydronornuciferine, mp 128–130°.

C. (±)-Nuciferine (4).—Dehydronuciferine and (±)-nuciferine were prepared exactly as described above under (±)-Nuciferine *via* the Oxidative Route.

(±)-**Glaucine** *via* **the Oxidative Route. A. 1-Veratrylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8).**—The tetrahydroisoquinoline **8** was prepared in the usual way (see the preparation of **6**, above) from 3.800 g (10 mmol) of 1-veratryl-3,4-dihydro-6,7-dimethoxyisoquinoline (**11**)[12] and 1.20 g (11 mmol) of ethyl chloroformate in a mixture of 100 ml of chloroform and 100 ml of 10% aqueous sodium carbonate solution. The product (**8**) was crystallized from methanol to give 2.90 g (70%) of white, shiny crystals, mp 154–155° (lit.[7a] mp 144–146°).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.52; H, 6.85; N, 3.31.

B. N-Carbethoxy-6a,7-dehydronorglaucine (14).—Irradiation of a solution of 0.4135 g (1.0 mmol) of 1-veratrylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**8**), 0.102 g (4.0 mmol) of iodine, and 0.200 g (1.0 mmol) of cupric acetate dihydrate in 700 ml of ethanol for 10 hr under a nitrogen atmosphere in the usual way gave 0.080 g (19%) of N-carbethoxy-6a,7-dehydronorglaucine: mp 162–163° (lit.[7a] mp 156–157°); λ_{max}^{EtOH} 272 (ε 60,900), 287 sh (ε 25,800), 322 (ε 13,200), 334 (ε 13,300), 353 (ε 2850), and 373 mμ (ε 1920).

Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.19; H, 6.30; N, 3.57.

C. Dehydroglaucine (17).—A solution of 0.0823 g (0.2 mmol) of N-carbethoxydehydroglaucine (**14**) in 1.0 ml of THF was treated with 1.0 ml of a reducing solution containing 0.6 mmol/ml of lithium aluminum hydride and 0.3 mmol/ml of aluminum chloride in THF. The reaction mixture was warmed at 50° for 0.5 hr and was then worked up in the usual way. The crude product was recrystallized from ethanol to give 0.052 g (73%) of dehydroglaucine: mp 115–116° (lit[14] mp 133–134°); λ_{max}^{EtOH} 264 (ε 47,000), 293 (ε 17,200), and 341 mμ (ε 10,600).

(19) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.17; H, 6.68; N, 3.97.

D. (±)-Glaucine (3).—Dehydroglaucine (0.052 g, 0.146 mmol) was reduced with 0.5 g of amalgamated zinc dust in the usual way [see (±)-nuciferine, above] to give *ca.* 0.048 g of (±)-glaucine, obtained as a pale yellow oil, identical in ir, uv, and R_f with an authentic sample of (+)-glaucine. Treating the oil with a solution of 0.030 g of picric acid in 25 ml of ethanol gave 0.061 g (71%) of the crystalline picrate, mp 197–199° dec (lit.[15] mp 193–194°).

(±)-Glaucine *via* the Dehydrohalogenation Route. A. 1-(2′-Bromo-4′,5′-dimethoxyphenyl)-N-(3,4-dimethoxyphenethyl)-acetamide.—A mixture of 13.75 g (0.05 mol) of 2-bromo-3,4-dimethoxyphenylacetic acid,[20] 10.0 g (0.55 mol) of 3,4-dimethoxyphenethylamine, and 100 ml of decalin was refluxed for 4 hr under nitrogen in a Dean–Stark apparatus. On cooling, the reaction mixture deposited a fine white precipitate which was recrystallized from ethanol to give 18.31 g (84%) of the desired phenylacetamide, obtained in two crops, mp 157–158° and 156–158°.

The analytical sample, mp 157.5–158.5°, was recrystallized from ethanol.

Anal. Calcd for $C_{20}H_{24}BrNO_5$: C, 54.80; H, 5.52; Br, 18.23; N, 3.20. Found: C, 54.76; H, 5.44; Br, 18.33; N, 3.22.

B. 1-(6′-Bromoveratryl)-6,7-dimethoxy-3,4-dihydroisoquinoline (12).—The above bromoamide (13.15 g, 0.03 mol) was mixed with 50 g of polyphosphate ester (PPE) and was heated for 18 hr at 95–100°. The reaction mixture was dissolved in 200 ml of tap water, and the resulting clear solution was washed once with ether and made basic with concentrated ammonium hydroxide. Extraction with chloroform, drying the extract over magnesium sulfate, and evaporation to dryness *in vacuo* gave approximately 13.0 g of the crude dihydroisoquinoline (12), which was used in the next step without further purification.

The dihydroisoquinoline 12 was analyzed in the form of its oxalate, a white microcrystalline solid, mp 192–193° (from methanol).

Anal. Calcd for $C_{22}H_{24}BrNO_8$: C, 51.78; H, 4.74; Br, 15.66; N, 2.74. Found: C, 51.57; H, 4.95; Br, 15.72; N, 2.78.

C. 1-(6′-Bromoveratrylidene)-N-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (9).—The crude dihydroisoquinoline prepared above (12, *ca.* 13.0 g) was dissolved in 200 ml of chloroform and the resulting clear solution was treated with 200 ml of 10% aqueous sodium carbonate solution and 16 ml of ethyl chloroformate while being stirred in a cold water bath at 15–20°. (The chloroformate was added in 2-ml portions during 0.75 hr.) The chloroform layer was separated, washed with dilute hydrochloric acid, dried over magnesium sulfate, and evaporated to give a solid residue. The residue was recrystallized from 1:1 chloroform–absolute ethanol to give the desired product (9), 9.96 g [67%, based on 1-(2′-bromo-4′,5′-dimethoxyphenyl)-N-(3,4-dimethoxyphenethyl)acetamide], mp 218.5–219.5°.

Anal. Calcd for $C_{23}H_{26}BrNO_6$: C, 56.11; H, 5.32; Br, 16.23; N, 2.84. Found: C, 55.96; H, 5.31; Br, 16.52; N, 2.93.

D. N-Carbethoxy-6a,7-dehydronorglaucine (14).—A mixture of the tetrahydroisoquinoline (9, 0.400 g, 0.814 mmol) and 0.5 g of calcium carbonate in 250 ml of anhydrous methanol was irradiated for 14 hr in the usual way. The reaction product was chromatographed twice on silica gel with chloroform [see section B of (±)-Nuciferine *via* the Dehydrogenation Route, above] and was recrystallized from absolute ethanol to give 0.080 g (24%) of N-carbethoxy-6a,7-dehydronorglaucine (14), mp 156–158°.

E. (±)-Glaucine (3).—Dehydroglaucine and (±)-glaucine were prepared exactly as described above under (±)-Glaucine *via* the Oxidative Route.

Registry No.—3, 5630-11-5; 4, 5868-18-8; 6, 22185-92-8; 7, 22185-85-9; 8, 22185-86-0; 9, 22185-87-1; 12 oxalate, 22212-25-5; 13, 13555-30-1; 14, 7630-72-0; 16, 7630-74-2; 17, 22212-26-6; 1-(2′-bromo-4′,5′-dimethoxyphenyl)-N-(3,4-dimethoxyphenethyl)acetamide, 22185-91-7.

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(20) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 1448 (1925).

The Structures of Herqueinone, Isoherqueinone, and Norherqueinone[1]

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A study of the nmr spectrum of the mold pigment herqueinone has revealed that it is a mixture of two stereoisomers, equilibratable in base. The more stable of these isomers is the substance which previously has been termed isoherqueinone. Mass spectra of many samples of highly purified herqueinone have revealed the persistent presence of variable amounts of desoxyherqueinone, of mass 16 less than herqueinone and having a markedly different fragmentation pattern. Herqueinone and desoxyherqueinone appear to form a charge-transfer complex which is less soluble than herqueinone, and whose separation from herqueinone has not been accomplished. Charge-transfer complexes have also been encountered between norherqueinone and desoxynorherqueinone (atrovenetin). All samples of norherqueinone that have been secured contained large amounts of desoxynorherqueinone, herqueinone, and desoxyherqueinone (mass spectra and nmr spectra). Although all other efforts to demonstrate a structural relationship between herqueinone and norherqueinone have failed, mass spectra have demonstrated the inferred relationship. Mass spectra also afforded evidence that the oxygen-containing ring in herqueinone is attached in the reverse sense to the originally reported structure.

Subsequent to the report[2] of the isolation of the copper-colored pigment herqueinone, preliminary investigations of the pigment were reported simultaneously by two groups of investigators.[3,4] In one of these reports[3] there was also described a second, very high-melting, insoluble red pigment, which could be converted to one of the trimethyl ethers of herqueinone by the same methylation procedure used for herqueinone. In view of this conversion, herqueinone, which contains one methoxyl group, was assumed to be a monomethyl ether of the second pigment. Since the name herqueinone had already been suggested,[5] the second pigment was termed nor-

(1) This investigation was supported in part by a research grant (G 24347) from the National Science Foundation. High-resolution mass spectra were determined on an instrument provided by a grant (GP 5323) from the National Science Foundation.

(2) F. H. Stodola, K. B. Raper, and D. I. Fennell, *Nature*, **167**, 773 (1951).

(3) J. A. Galarraga, K. G. Neill, and H. Raistrick, *Biochem. J.*, **61**, 456 (1955).

(4) R. H. Harman, J. Cason, F. H. Stodola, and A. L. Adkins, *J. Org. Chem.*, **20**, 1260 (1955).

(5) Prior correspondence between Stodola, Raistrick, and Cason had resulted in agreement on simultaneous submission of the preliminary investigations, as well as certain details such as nomenclature.