Synthesis and Photolysis of Kreysiginone

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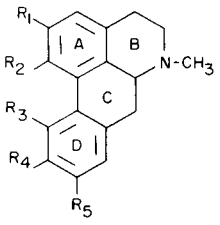
In 1967, two new classes of alkaloids were discovered by Battersby and coworkers (1,2), both homologs of the aporphine and proaporphine series. These compounds represented new members of the 1-phenethyltetrahydroisoquinoline class of alkaloids and were given the names homoproaporphines (**1**) and homoaporphines (**2**). Floramultine (**2a**), multifloramine (**2b**), and kreysigine (**2c**) are thus the first examples of homoaporphine alkaloids and their occurrence in *Kreysigia multifora* is of significant interest since colchicine has recently been detected in this plant. By chromatographic examination of the minor alkaloids of *K. multifora*, Battersby isolated kreysiginone (**1a**), the first member of the homoproaporphine class of alkaloids.



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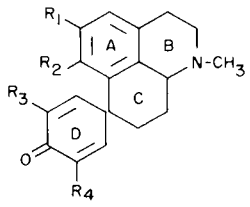


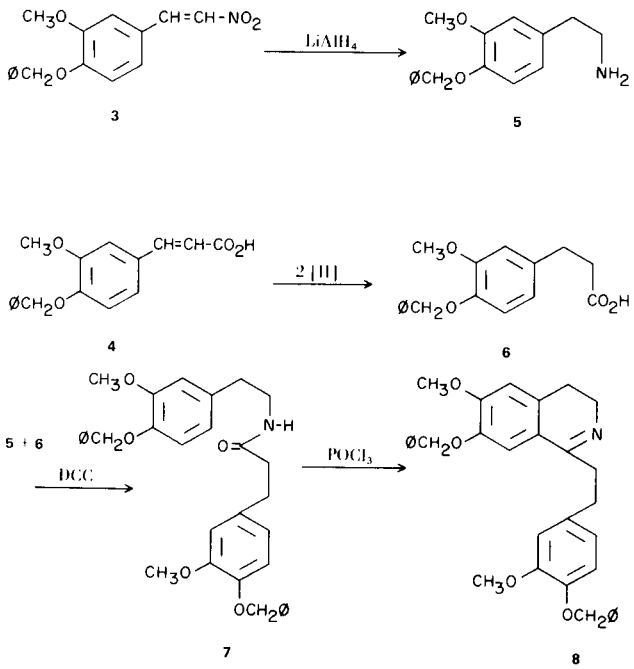
1

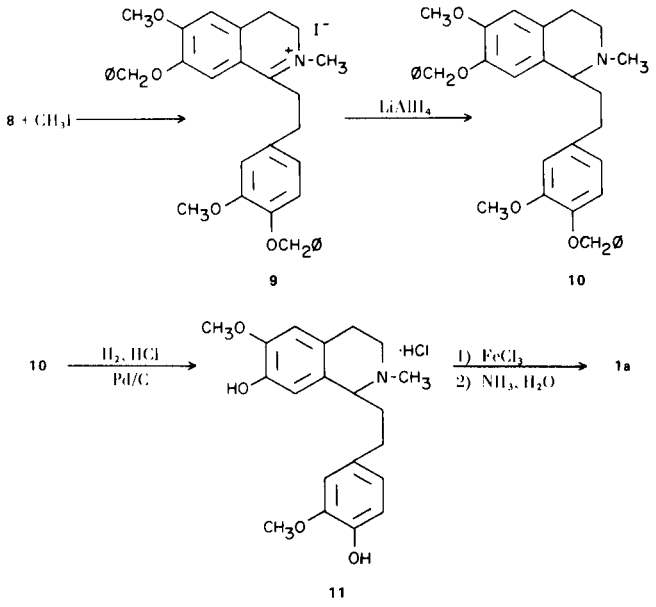
2a, R_1 R_3 R_4 OCH_3, R_2 R_5 OH
2b, R_1 R_3 R_5 OCH_3, R_2 R_4 OH
2c, R_1 R_3 R_4 R_5 OCH_3, R_2 OH

1a, R_1 R_3 OCH_3, R_2 OH, R_4 H

Recently, Kametani and coworkers (3) reported the first synthesis of kreysiginone (**1a**). However, this scheme involved many intermediates with unsatisfactory elemental analyses and poor or no reported yields. Also involved during the course of this synthesis was the replacement of protecting groups which had been cleaved inadvertently while certain reactions were being carried out.

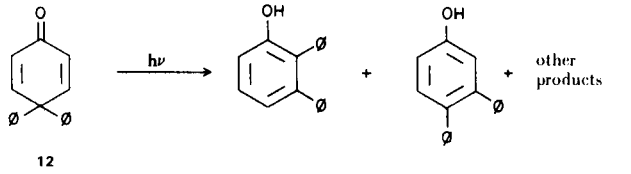
Because of the great importance of this new class of alkaloids, we have devised a new and elegant synthesis of kreysiginone (**1a**). The starting materials for this synthetic sequence were 4-benzyloxy-3-methoxy-β-nitrostyrene (**3**) (4) and 4-benzyloxy-3-methoxycinnamic acid (**4**) (5). Treatment of **3** with lithium aluminum hydride afforded β-(4-benzyloxy-3-methoxyphenyl)ethylamine (**5**) in 60% yield (6). A preparative electrolytic method was used to reduce the cinnamic acid **4** to β-(4-benzyloxy-3-methoxyphenyl)propionic acid (**6**) in 90% yield. Both of these reduction methods left the benzyl ether moiety intact. Compounds **5** and **6** were then condensed in the presence of *N,N*-dicyclohexylcarbodiimide (DCC), giving a 56% yield of *N*-(4-benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-methoxyphenylpropionamide (**7**). Cyclodehydration of the amide **7** by using the Bischler-Napieralski reaction conditions afforded a quantitative yield of 7-benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**8**). Treatment of **8** with methyl iodide afforded **9** which was subsequently reduced with lithium aluminum hydride to give 78% yield of 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (**10**) which was isolated and characterized as its oxalate salt derivative. Removal of the benzyl groups in **10** was accomplished by catalytic hydrogenation in the presence of hydrochloric acid using 10% palladium on charcoal. The resulting 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline hydrochloride (**11**) was subjected to a phenolic oxidative coupling reaction using ferric chloride. A lengthy workup including column chromatography over Silica Gel G yielded colorless crystals (12%), m.p. 190-192°, which were subsequently identified as kreysiginone (**1a**) by undepressed mixed melting point and superimposable ir spectra when compared with the authentic sample.



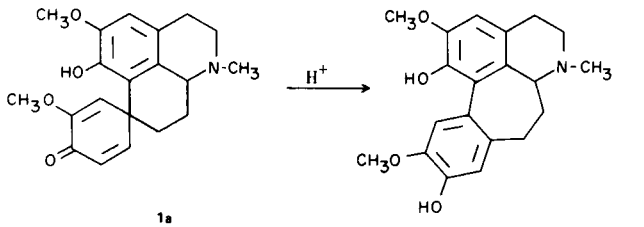


Photolysis of Kreysiginone (**1a**).

Numerous examples for the photochemical rearrangement of dienones have appeared in the literature (8). One system which has been extensively studied by Zimmerman, *et al.* (9) is represented by 4,4-diphenylcyclohexadienone (**12**). Irradiation of this compound afforded several products, but most notably, were the structures resulting from a dienone-phenol rearrangement.

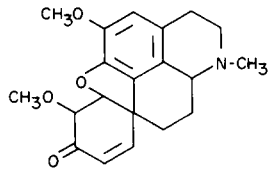


Kreysiginone (**1a**), which possesses a spiro-dienone D ring, has been shown to undergo a dienone-phenol rearrangement in an acidic media (2,10), to yield a homoaporphine with a phenolic D ring.



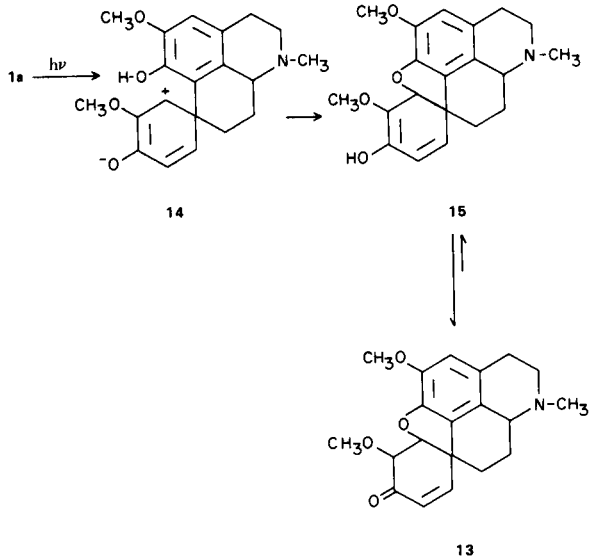
Until now, no attempt has been made to study the photochemical rearrangement of kreysiginone, a naturally occurring product. After the total synthesis of kreysiginone, this compound was irradiated for 69 hours in the absence of acid. A lengthy workup of the reaction mixture yielded a small amount of product which was characterized by spectral data and a possible structure was proposed.

The infrared spectra showed an intense carbonyl (C=O) stretching at 1690 cm^{-1} as compared to 1660 cm^{-1} for the starting material. However, no hydroxyl group absorption was noted in this spectra. A shift to shorter wavelength (276 mμ) and a smaller molar extinction coefficient for this wavelength (ϵ 1,510) was shown in the ultraviolet spectrum. The nuclear magnetic resonance spectrum showed the following fragmentations: m/e 341 (M^+), (M^+-1), (M^+-17), (M^+-28), (M^+-29), (M^+-43). Since the starting material used was of one epimeric form (the higher melting epimer with the stereochemistry (10) as shown for **1a**), and on the basis of the spectral data and elemental analysis the following structure is proposed for the photolysis product **13**.



Considering the reaction conditions and the mechanism for the photolytic rearrangement of dienones, the formation of **13** can be rationalized. Chapman (8) has stated that excitation of the α,β-unsaturated ketone moiety of a molecule involves electron redistribution which can be represented as a dipolar system. Thus, the excited state of

Scheme I



kreysiginone could be represented by structure **14**. Subsequently, a 1,4-Michael type addition could take place giving rise to **15**. By tautomeric shift, the keto-structure **13** would be formed from the enol **15**. The formation of 1,2,3,6a,7,11,12,12a-octahydro-5,7-dimethoxy-1-methyl-8*H*-benzo[2,3]benzofuro[5,4,3-*def*]quinolin-8-one (**13**) can be explained by the mechanism proposed in Scheme I.

EXPERIMENTAL

The melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to record the infrared (ir) spectra. The ultraviolet (uv) spectra were taken in 95% ethanol on a Carey-14 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using deuteriochloroform or hexadeuteriodimethylsulfoxide as solvents using tetramethylsilane (TMS) as an internal standard. Mass spectral data were obtained on an Atlas CH-4 mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee and Midwest Microlab, Inc., Indianapolis, Indiana. A Rayonet Photochemical Reactor with a pyrex filter was used for photolysis of kreysiginone. A Sorensen DCR-150-15A power supply was used in the electrolytic reduction. A 6 ft. 10% SE Column connected to a Hewlett-Packard gas chromatograph was used for glc analysis. Silica Gel-G from Brinkman Instruments was used for thin-layer chromatography (tlc) either on glass slides or 6 x 20 cm. glass plates. Silica Gel-G was also used for preparative thin-layer chromatography on 20 x 20 cm. glass plates. Spots on plates were detected by iodine vapor. Column chromatography was carried out on a 2 x 40 cm. glass column packed with Silica Gel using chloroform containing 1% methanol as the eluting solvent mixture.

Preparation of Starting Materials.

4-Benzyloxy-3-methoxybenzaldehyde.

This compound was prepared by the procedure of Buzas and Dufour (11) in 85% yield, m.p. 60-62° (lit. (11) m.p. 63-64°); ir (nujol) 1675 cm^{-1} (C=O); nmr (deuteriochloroform), τ 6.10 (s, 3, OCH_3), 4.8 (s, 2, OCH_2), 2.0 (m, 8, Ar*H*), 0.10 (s, 1, *H*C=O).

4-Benzyloxy-3-methoxy-β-nitrostyrene (**3**).

This compound was prepared by the procedure of Lange and Hambourger (4) in 67% yield, m.p. 122-123° (lit. (4) m.p. 122-123°); nmr (deuteriochloroform), τ 6.06 (s, 3, OCH_3), 4.6 (s, 2, OCH_2), 2.80 (m, 8, Ar*H* and C*H*), 2.06 (d, 1, J = 14 cps, C*H*).

4-Benzyloxy-3-methoxycinnamic Acid (**4**).

This compound was prepared according to the procedure of Pearl and Beyer (5), in 84% yield, m.p. 189-191° (lit. (5) m.p. 191°); ir (nujol) 1670 cm^{-1} (C=O); nmr (DMSO-d_6), τ 6.14 (s, 3, OCH_3), 4.84 (s, 2, OCH_2), 3.54 (d, 1, J = 16 cps, C*H*), 2.60 (m, 9, C*H* and Ar*H*).

β-(4-Benzyloxy-3-methoxyphenyl)ethylamine (**5**).

A modified procedure of Konodo and coworkers (6) was used for the preparation of this compounds.

Under an atmosphere of nitrogen gas, dry tetrahydrofuran (500 ml.) and lithium aluminum hydride (35.0 g., 0.9 mole) were placed in a 3-l. three necked round bottom flask fitted with a stirrer, reflux condenser (protected from moisture) and an addition funnel. 4-Benzyloxy-3-methoxy-β-nitrostyrene (**3**, 57.0 g., 0.2 mole) was dissolved in dry tetrahydrofuran (1500 ml.) and added dropwise at such a rate as to maintain reflux. After the addition was complete (2 hours), the solution was refluxed for another 24 hours. This mixture was then cooled in an ice-salt bath and to it was added successively water (35 ml.), aqueous sodium hydroxide (40 ml., 15%) and water (105 ml.) over a period of several hours under a continous stream of nitrogen gas. The precipitated salts were then collected by filtration and washed with tetrahydrofuran (500 ml.). The combined filtrate and washings were concentrated under reduced pressure. The residue was cooled and to it was added hydrochloric acid (200 ml., 10%) and enough water to just dissolve the salt formed. Organic impurities were removed by extracting this water solution with ether (300 ml.). The organic layer was discarded while the aqueous layer was cooled and made strongly basic with 40% aqueous sodium hydroxide solution. This mixture was then extracted with ether (1000 ml.) and dried over potassium carbonate. Filtration and evaporation of this ethereal solution yielded β-(4-benzyloxy-3-methoxyphenyl)ethylamine (**5**, 30.6 g., 56%) as a thick oil which was sufficiently pure for further reactions. Crystallization of this oil from benzene-petroleum ether (b.p. 30-60°) gave white needles, m.p. 59-62°, lit. (6) m.p. 65-80°. β-(4-Benzyloxy-3-methoxyphenyl)ethylamine hydrochloride, m.p. 173°, lit. (7) m.p. 173-175°; ν max (chloroform), (cm^{-1}) 3400-3100 (NH_2); nmr (deuteriochloroform), τ 8.64 (s, 2, NH_2), 7.25 (m, 4, CH_2), 6.18 (s, 3, OCH_3), 4.92 (s, 2, OCH_2), 3.25 (m, 3, Ar*H*), 2.66 (m, 5, Ar*H*).

β-(4-Benzyloxy-3-methoxyphenyl)propionic Acid (**6**).

Apparatus.

The reduction was carried out in a 4 l. beaker immersed in cold water for cooling. The cathode for the reaction was a mercury pool at the bottom of the beaker, while a strip of lead sheet suspended in a porous cup served as the anode. The current used for this experiment was provided by a Sorenson power supply. The reaction was run in such a manner so that the mechanical stirring was provided for the catholyte.

Reduction.

4-Benzyloxy-3-methoxycinnamic acid (**4**, 100 g., 0.35 mole) was added with stirring to a solution of aqueous sodium sulfate (1000 ml., 7%) placed in the beaker and the porous cup. An aqueous solution of sodium hydroxide (15 g. in 75 ml. of water) was then added slowly until most of the acid had dissolved. The current was started and maintained at 8 amperes for 8 hours while the solution in the porous cup was kept basic by frequent additions of a concentrated sodium hydroxide solution. When reduction was complete, the cathode solution was decanted from the mercury pool, collected by filtration and acidified with concentrated sulfuric acid. The precipitate was collected by filtrate, washed with water (200 ml.) and dried. White crystals (90.0 g., 90%) of β-(4-benzyloxy-3-methoxyphenyl)propionic acid (**6**) were obtained by recrystallization from benzene-petroleum ether (b.p. 30-60°), m.p. 93-95°, (lit. (7) m.p. 98-99°); ir (nujol) 1700 cm^{-1} (C=O); nmr (DMSO-d_6); τ 7.20 (m, 4, CH_2), 6.14 (s, 3, OCH_3), 4.88 (s, 2, OCH_2), 3.26 (m, 3, Ar*H*), 2.60 (m, 5, Ar*H*), -0.98 (s, 1, CO_2H).

N-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-methoxyphenylpropionamide (**7**).

β-(4-Benzyloxy-3-methoxyphenyl)ethylamine (**5**, 10.3 g., 40 mmoles) and β-(4-benzyloxy-3-methoxyphenyl)propionic acid (**6**, 11.4 g., 40 mmoles) were dissolved in methylene chloride (200 ml.) and cooled to 0°. To this stirred and cold solution was added,

N,N-dicyclohexylcarbodiimide (8.3 g., 42 mmoles) in methylene chloride (50 ml.) over a period of 30 minutes. The reaction mixture was allowed to stir at 0° for 20 hours. Filtration of the precipitated urea and evaporation of the solvent afforded a tan product which after recrystallization from 95% ethanol gave colorless crystals (11.7 g., 56%) of **17**, m.p. 135°. The analytical sample was obtained by four recrystallizations from 95% ethanol, m.p. 136-137°; ir (nujol) 3310 (N–H), 1650 cm^{-1} (C=O); nmr (deuteriochloroform), τ 7.00 (m, 8, CH_2), 6.18 (s, 6, OCH_3), 4.88 (s, 4, OCH_2), 4.32 (s, 1, N*H*), 3.30 (m, 6, Ar*H*), 2.60 (m, 10, Ar*H*); uv (95% ethanol) 229 mμ (ϵ, 14,500).

Anal. Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.66. Found: C, 75.71; H, 6.56; N, 2.58.

7-Benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**8**).

N-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3-methoxyphenylpropionamide (**7**, 12.0 g., 23 mmoles) and phosphorus oxychloride (55 g., 280 mmoles) were refluxed for 1 hour in dry benzene (200 ml.). The solvent was removed under reduced pressure and the residue taken up in chloroform (250 ml.). The chloroform solution was then washed with two portions of 10% aqueous ammonia (100 ml.), two portions of water (50 ml.) and dried over sodium sulfate. Evaporation of the solvent left a tan oil, which was crystallized from a 10:1 hexane-benzene solution to give **8** (11.5 g., 99%) as tan crystals. Compound **8** was found to be analytically pure as white needles, m.p. 89.5-90.8°, after four recrystallizations from hexane-benzene. Its hydrochloride salt derivative melted at 195-197°; ir (nujol) 1640, 1575 cm^{-1} (C=N); uv (ethanol) 230 mμ (ϵ, 12,600); nmr (deuteriochloroform), τ 7.40 (m, 2, CH_2), 7.10 (s, 4, CH_2), 6.38 (s, 2, CH_2), 6.08 (s, 3, OCH_3), 6.12 (s, 3, OCH_3), 4.84 (s, 4, OCH_2), 3.20 (m, 4, Ar*H*), 2.92 (s, 1, Ar*H*), 2.56 (m, 10, Ar*H*).

Anal. Calcd. for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.75. Found: C, 78.31; H, 6.27; N, 2.70.

7-Benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (**9**).

4-Benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**8**, 4.75 g., 9.5 mmoles) and methyl iodide (1.35 g., 9.5 mmoles) were dissolved in benzene (75 ml.) and allowed to stand at room temperature for 24 hours. The yellow salt which separated out was collected by filtration, washed with cold benzene (20 ml.) and recrystallized from acetone to give **9** (6.1 g., 100%) as pale yellow needles, m.p. 131-133°. An analytical sample was prepared by three recrystallizations of **9** from dry acetone, m.p. 131-133°; ir (nujol) 1650, 1570 cm^{-1} (C=N); nmr (deuteriochloroform), τ 7.84 (s, 2, NCH_3), 6.80 (m, 8, CH_2), 6.15 (s, 3, OCH_3), 6.05 (s, 3, OCH_3), 4.89 (s, 2, OCH_2), 4.83 (s, 2, OCH_2), 3.30 (m, 5, Ar*H*), 2.60 (m, 10, Ar*H*).

Anal. Calcd. for $C_{34}H_{36}INO_4$: C, 62.86; H, 5.58; N, 2.15. Found: C, 62.87; H, 5.57; N, 2.06.

7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenoxyphenethyl)-6-methoxy-2-methylisoquinoline Oxalate (**10**).

7-Benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline methiodide (**9**, 13.0 g., 20 mmoles) was added to a stirred solution of lithium aluminum hydride in absolute ether (550 ml.) over a period of 2 hours. Stirring was continued at room temperature for 30 minutes. The reaction mixture was cooled in an ice-salt bath and, under an atmosphere of nitrogen gas, water (5 ml.), sodium hydroxide (5 ml., 15%) and water (15 ml.) were added, respectively. The salts were removed by filtration and the water separated from the ether. The ethereal solution was dried over potassium carbonate and, with vigorous stirring, a saturated ethereal solution of oxalic acid was slowly added. The compound **10** separated rapidly as an oil which soon solidified after scratching and cooling. After filtration and recrystallization from methanol-ether the product (**10**, 9.6 g., 78%) was obtained as clumps of white crystals, m.p. 105-109° (effervescence). An analytical sample was prepared by three recrystallizations from methanol-ether, m.p. 112° (effervescence); ir (nujol) 1700 (C=O) cm^{-1}; nmr (deuteriochloroform), τ 7.80-7.40 (m, 9, CH_2), 7.22 (s, 3, NCH_3), 6.16 (s, 6, OCH_3), 4.92 (s, 2, OCH_2), 4.88 (s, 2, OCH_2), 3.30 (m, 5, Ar*H*), 2.62 (s, 10, Ar*H*), −1.18 (s, 1, CO_2H); uv (95% ethanol) 283 mμ (ϵ, 6,700), 230 mμ (ϵ, 19,000).

Anal. Calcd. for $C_{36}H_{39}NO_8$: C, 70.46; H, 6.41; N, 2.28. Found: C, 70.36; H, 6.47; N, 2.24.

1,2,3,4-Tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline Hydrochloride (**11**).

7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline oxalate (**10**, 9.6 g.) was dissolved in 10% sodium hydroxide solution (100 ml.) and extracted with chloroform (200 ml.). After drying over potassium carbonate followed by filtration and evaporation, 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-benzyloxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (7.5 g., 14.1 mmoles) was obtained. This material was then dissolved in methanol (250 ml.) containing palladium on charcoal (0.7 g., 10%) and concentrated hydrochloric acid (5 ml.). Hydrogenation was carried out at an initial pressure of 40 psi for 18 hours. The solution was filtered through Celite and the solvent removed *in vacuo* to leave **11** as a colorless oil. This compound crystallized from benzene-methanol-ether as a solvate of benzene to leave 4.8 g. (90%) of white crystals, m.p. 110° (effervescence). It was also recrystallized from acetonitrile to give colorless needles of the solvate, m.p. 103° (effervescence). Two separate analytical samples were prepared; one from benzene-methanol-ether and one from acetonitrile. In each case four recrystallizations were necessary; ir* (chloroform), 3400 cm^{-1} (OH); nmr (DMSO-d_6), τ (benzene solvate) 8.0-5.6 (m, 8, CH_2), 7.24 (s, 3, NCH_3), 6.24 (s, 6, OCH_3), 3.20 (m, 5, Ar*H*), 2.60 (s, 2, benzene), 1.20 (s, 1, O*H*), 0.80 (s, 1, O*H*); nmr (DMSO-d_6), τ (acetonitrile solvate) 8.0 (s, 2, acetonitrile), 8.0-5.6 (m, 8, CH_2), 7.24 (s, 3, NCH_3), 6.24 (s, 6, OCH_3), 3.20 (m, 5, Ar*H*), 1.20 (s, 1, O*H*), 0.80 (s, 1, O*H*); uv* (95% ethanol) 284 mμ (ϵ, 6,700), 229 mμ (ϵ, 13,100). *(Both solvates.)

Anal. Calcd. for $C_{20}H_{26}ClNO_4 \cdot 1/5\ C_6H_6$: C, 64.38; H, 6.93; N, 3.54. Found: C, 64.24; H, 7.20; N, 3.40.

Anal. Calcd. for $C_{20}H_{26}ClNO_4 \cdot 3/4\ CH_3CN$: C, 62.88; N, 6.93; N, 5.96. Found: C, 62.98; H, 7.05; N, 5.76.

Phenolic Oxidation of **11**: Preparation of Kresiginone (**1a**).

A solution of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxy-2-methylisoquinoline hydrochloride (**11**, 4.5 g., 11.8 mmoles) in degassed water (200 ml.) was added, under nitrogen gas, dropwise to a solution of ferric chloride (19.2 g., 720 mmoles) in degassed water (100 ml.). Stirring was continued for 3.5 hours and the solution made strongly basic with 28% ammonium hydroxide. The resulting brown gel was filtered through Celite and then washed with chloroform (800 ml.). The filtrate was extracted with chloroform (200 ml.). The chloroform extracts were combined, dried (sodium sulfate) and filtered. Evaporation left a brown oil (2.0 g.) which was chromatographed over Silica Gel (30 g.) and eluted with 1% methanol in chloroform. Twelve 50 ml. fractions were collected. Fractions 5 through 10

contained the dienone **1a**. Recrystallization of this oil from hexane containing a small amount of chloroform gave colorless crystals of **1a** (0.55 g., 12%) m.p. 190-192°, lit. (3) m.p. 193-195°. A mixed melting point of the crystals with an authentic sample of the dienone, prepared by the procedure of Kametani, *et al.* (3) showed no depression and the infrared spectra (chloroform) of the two samples were superimposable; ir (chloroform), 3505 (OH), 1660 (C=O), 1640 (C=C), 1610 cm^{-1} (C=C); uv (95% ethanol) 286 mμ (ϵ, 13.500), 244 mμ (ϵ, 6,500); nmr (deuteriochloroform), τ 8.00-6.00 (m, 9, C*H*, CH_2) 7.58 (s, 3, NCH_3), 6.38 (s, 3, OCH_3), 6.24 (s, 3, OCH_3), 4.33 (m, 1, =C*H*), 3.85 (m, 1, =C*H*), 3.00 (m, 1, C*H*), 3.42 (m, 1, Ar*H*).

Photolysis of Kresiginone (**1a**).

Kresiginone (**1a**, 150 mg., 0.44 mmole) was dissolved in thiophene free benzene (150 ml.) and argon was passed through the solution for 2 hours. The mixture was then photolyzed for 69 hours using a Rayonet Photochemical reactor with a pyrex filter. Thin-layer chromatography was used to monitor the reaction using methanol-chloroform (1:3) as the developing solvents. After the reaction was essentially complete the solution was evaporated to a dark oil. This oil was then subjected to preparative thin-layer chromatography using three 20 x 20 cm. glass plates with a 0.5 mm. coating of Silica Gel-G and methanol-chloroform (1:3) as the developing solvents. Five major bands were detected by iodine vapor. However, only the band at R_f 0.7-0.8 contained a significant amount of any material. After a second preparative thin-layer chromatography of this fraction, 15 mg. of a light yellow non-crystalline material was obtained which darkened rapidly when exposed to air and light. An analytical sample of **13** was obtained by chromatography over 10 g. of Silica Gel using 1% methanol in chloroform as the eluting solvents; ir (chloroform), 1690 cm^{-1} (C=O); nmr (deuteriochloroform), τ 7.60 (s, 3, NCH_3), 7.00 (m, 8, CH_2), 6.37 (s, 3, OCH_3), 6.16 (s, 3, OCH_3), 3.99 (m, =C*H*), 3.54 (s, 1, Ar*H*); uv (95% ethanol) 276 mμ (ϵ, 1,510); mass spectrum m/e 341 (M^+), (M^+-1), (M^+-17), (M^+-28), (M^+-29), (M^+-43).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.37; H, 6.78; N, 4.10. Found: C, 71.02; H, 7.09; N, 3.68.

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