water, the reaction mixture was treated in a similar manner to that of the above compound (**3**) to give 11 mg (1.6%) of 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril as colorless plates, which were identical with the authentic sample described before.

1-(2-Amino-4-hydroxy-3,5-dimethoxyphenethyl)-7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (18).—A mixture of 7 g (12.3 mmol) of **13**, 140 ml of ethanol, and 140 ml of concentrated hydrochloric acid was refluxed for 3 hr. The reaction mixture was treated in the same manner as in the case of **16** to give 4.2 g of **18** as a brown viscous syrup, which was purified by chromatography on 100 g of silica gel using chloroform containing 1% methanol as an eluent. Evaporation of the appropriate fraction gave 1.2 g (25%) of **18** as a viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.60 (3, s, NCH_3), 6.25 (3, s, OCH_3), 6.19 (6, s, $2OCH_3$), 3.67 (1, s, 6′ H), 3.51 (2, s, 5 H and 8 H). This was labile in air and therefore used immediately.

Photolysis of the Diazonium Salt of 18.—A solution of diazonium salt [prepared from 1.2 g (3.1 mmol) of diphenolic isoquinoline **18**, 70 ml of 1 *N* sulfuric acid, 10 ml of glacial acetic acid, and 214 mg (3.1 mmol) of sodium nitrite] was diluted to a volume of 1 l. which was irradiated with a Hanovia 450-W mercury lamp under the same conditions as in the case of **3**. The crude product (520 mg) was chromatographed on 15 g of silica gel using chloroform containing 1% methanol as an eluent inspecting with thin layer chromatography, infrared and ultraviolet spectra. Evaporation of the appropriate fraction gave 180 mg (15%) of homoproaporphine (**20**): mp 176–178° (lit.[8] mp 176–178°); infrared hydroxy group at 2.86 (s), enone C=C at 6.06 (s) and 6.18 μ (s); ultraviolet 232 and 278 nm (log ϵ 4.04 and 4.03); nmr spectrum τ 7.65 (3, s, NCH_3), 6.44 (3, s, OCH_3), 6.37 (3, s, OCH_3), 6.22 (3, s, OCH_3), 4.14 and 4.0 (2, each d, J = 2.5 Hz, olefinic protons), 3.57 (1, s, aromatic proton). These spectral data were superimposable upon those of an authentic sample (**20**).[8]

Registry No.—**2**, 31730-26-4; **5**, 31836-46-1; **6**, 31730-27-5; **8**, 31735-04-3; **8** methiodide, 31735-03-2; **10**, 31735-05-4; **11** 31735-06-5; **11** HCl, 31735-11-2; **12**, 31735-07-6; **13**, 31735-08-7; **16**, 31735-09-8; **18**, 31735-10-1.

Acknowledgments.—We thank Professor F. Šantavý, The Chemical Institute, Palacky University for a gift of androcymbine. We also thank Miss R. Kato, Miss A. Kawakami, Miss R. Suzuki, Miss U. Tadano, Miss T. Yoshida, Miss C. Yoshida, and Mr. T. Ohuchi for microanalyses and spectral measurements.

Studies on the Syntheses of Heterocyclic Compounds. CDLI. Alternative Photolytic Total Syntheses of *O*-Methylandrocymbine and Kreysigine

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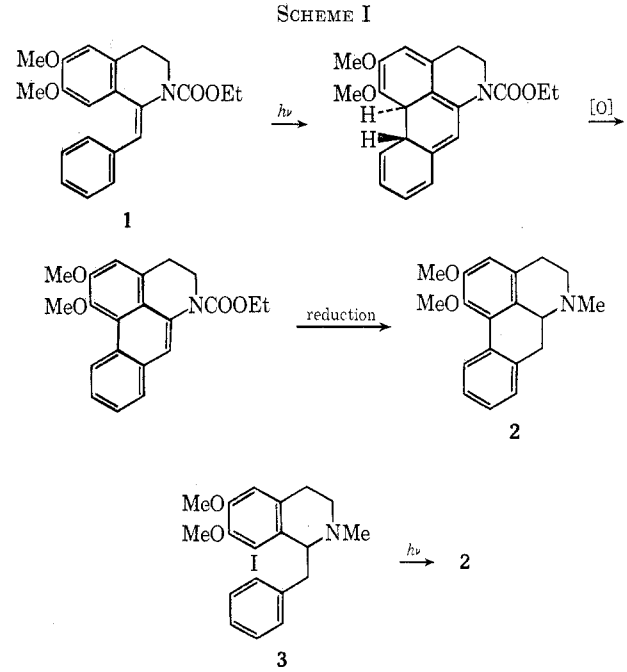
The total syntheses of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) by photolysis of 1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**) are reported. The same reaction of the demethoxy analog **13a** to the homomorphinandienone **14** and homoaporphine **15** is also described.

Photolytic electrocyclic reactions[1] have constituted the backbone of the synthesis of the cyclic compounds by carbon–carbon bond formation and are extremely useful in natural product synthesis.[2] These useful reactions involve cyclization of conjugated olefinic systems and have been applied to the photolytic synthesis of aporphine alkaloids,[3] as shown in the total synthesis of (±)-nuciferine (**2**) from the substituted stilbene **1**.[4]

Moreover, Kupchan[5] reported a new application of the photolytic cyclization of iodoaromatic compounds (**3**) in an intramolecular reaction in order to accomplish the synthesis of (±)-nuciferine (**2**) (Scheme I).

We achieved the photolytic conversion of the diazotized isoquinoline **4** to the morphinandienone **6**[6] in addition to the aporphine **7** and applied this reaction to the synthesis of (±)-*O*-methylandrocymbine (**8**).[7] In this reaction, an aromatic radical **5** formed by the decomposition of a diazonium group participates in the coupling reaction of both aromatic rings.[8] Therefore,

SCHEME I

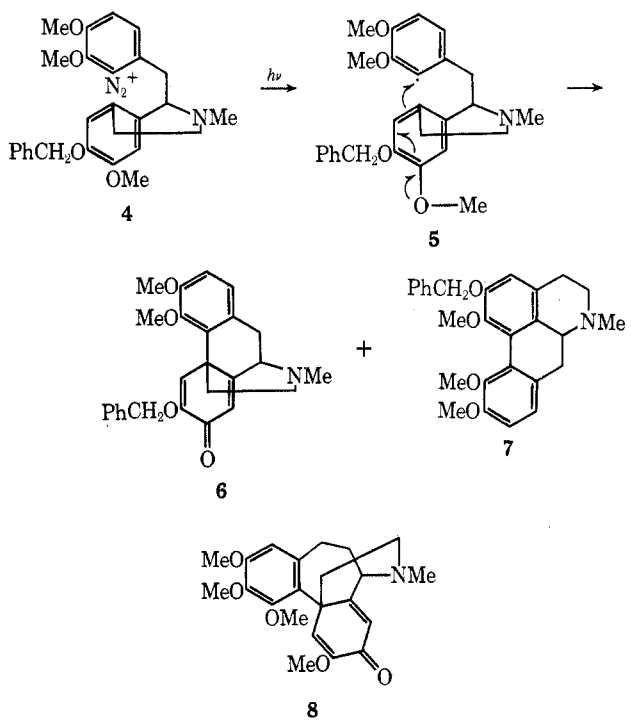


we examined the photolysis of the bromoisoquinoline. Herein we wish to report the syntheses of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) (Scheme II).

Since the formation of a seven-membered-ring system by a radical coupling reaction is not so easy, the pre-

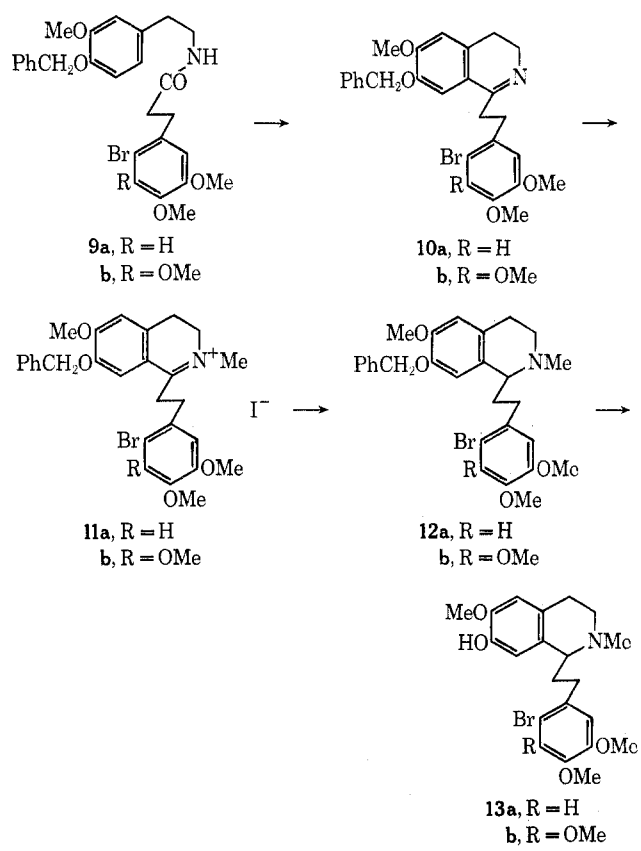
(1) R. B. Woodward and R. Hoffmann, "The Conversion of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(2) P. G. Sammers, *Quart. Rev. Chem. Soc.*, **24**, 37 (1970).
(3) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).
(4) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *ibid.*, 2937 (1966).
(5) S. M. Kupchan and R. M. Kanojia, *ibid.*, 5353 (1966).
(6) T. Kametani, K. Fukumoto, and K. Shishido, *Chem. Ind. (London)*, 1566 (1970).
(7) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Commun.*, 1157 (1970).
(8) A. Schonberg, "Preparative Organic Photochemistry," Springer-Vorlag, New York, N. Y., 1968, p 313, and references cited therein.

SCHEME II



liminary experiment was carried out as follows using material easily available; namely, 2′-bromophenolic isoquinoline (**13a**) was synthesized from 2-bromo-4,5-dimethoxyphenylpropionic acid[9] and 4-benzyloxy-3-methoxyphenethylamine in the usual way (see Scheme III and Experimental Section).

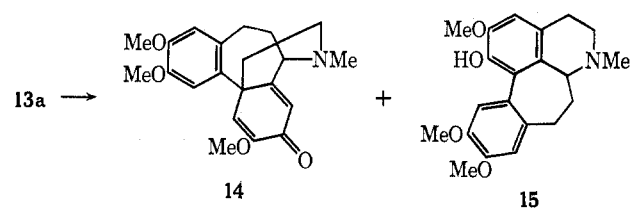
SCHEME III



(9) H. G. Graftree and R. Robinson, *J. Chem. Soc.*, **113**, 871 (1918).

Irradiation of **13a** with a Hanovia 450-W mercury lamp surrounded by a Pyrex filter in ethanolic sodium hydroxide aqueous solution at room temperature for 7 hr gave two compounds. Purification on silica gel column chromatography showed that the first one, characterized as its methiodide, could be assigned to the homomorphinandienone **14** by comparison of spectroscopic data with an authentic sample.[10] The second compound, $C_{21}H_{25}O_4N$, *m/e* 355 (M^+), showed a typical homoaporphine system in its uv spectrum[11,12] (λ_{max} 262.5 and 290 nm). This hypothesis was supported by mass spectrum[12] revealing an ion at *m/e* 388 ($M^+ - OH$, base peak) and also by nmr spectrum[11] showing three aromatic protons resonanced at τ 3.43, 3.27, and 2.92. Therefore, the second compound was assigned as 1-hydroxy-2,10,11-trimethoxyhomoaporphine (**15**) (Scheme IV).

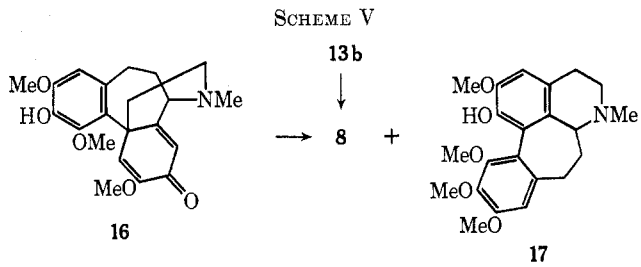
SCHEME IV



Thus, we developed a new synthetic route to the homomorphinandienone and homoaporphine type compounds which have the basic skeleton of the alkaloids found in *Liliaceae* species.[13]

Total Syntheses of (±)-*O*-Methylandrocymbine (8) and (±)-Kreysigine (17).—The above synthesis of the homomorphinandienone **14** and homoaporphine **15** should function, in principle, also with 1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**), thus leading to the total synthesis of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) (Scheme V).

SCHEME V



The starting phenolic isoquinoline **13b** was synthesized from 2-bromo-3,4,5-trimethoxyphenylpropionic acid[14] by the usual method. Photolysis of **13b**, under conditions similar to the reaction of **13a**, yielded two components in addition to the starting material. The first one was identical with *O*-methylandrocymbine (**8**)[7] prepared from natural androcymbine (**16**) by spectral

(10) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc. C*, 3084 (1968).

(11) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *ibid.*, 1003 (1968); 382 (1970).

(12) A. R. Battersby, R. B. Bradbury, R. G. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 450 (1967).

(13) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa, Tokyo, and Elsevier, Amsterdam, 1968, pp 222 and 258.

(14) H. F. Frank, P. E. Fanta, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **70**, 2314 (1948).

comparisons. The second compound, which showed the same molecular formula, $C_{22}H_{27}O_5N$, as *O*-methylandrocymbine, was assigned (±)-kreysigine (**17**), an alkaloid found in *Kreysigia multiflora*,[12] by comparison of spectroscopic data with those of the authentic sample[15] prepared by a photo-Pschorr reaction.

Thus, we achieved the alternative syntheses of (±)-*O*-methylandrocymbine and (±)-kreysigine in similar yields. The photolysis of the phenolic bromo aromatic compounds would be a useful method for the synthesis of the dienone type compound such as salutaridine.[16]

Experimental Section[17]

N-(**4-Benzyloxy-3-methoxyphenethyl**)-**3**-(**2-bromo-4,5-dimethoxyphenyl**)**propionamide** (**9a**).—A mixture of 8 g of 4-benzyloxy-3-methoxyphenethylamine and 8.7 g of 2-bromo-4,5-dimethoxyphenylpropionic acid was heated at 190° for 1 hr and the mixture was extracted with chloroform. The extract was washed with 10% sodium hydroxide and water and dried over sodium sulfate. Evaporation of the solvent gave 15.5 g of **9a** as colorless needles, mp 150–152° (from methanol), $\nu_{max}^{CHCl_3}$ 3400 (NH) and 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{30}BrNO_5$: C, 61.41; H, 5.73; N, 2.65. Found: C, 61.61; H, 5.60; N, 2.84.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**10a**).—A mixture of 11 g of the preceding amide, 7 g of phosphoryl chloride, and 100 ml of dry benzene was refluxed for 1.5 hr. The precipitate was collected and recrystallized from methanol to give 9 g of the isoquinoline **10a** hydrochloride, mp 210–212°, $\nu_{max}^{CHCl_3}$ 1650 (>C=N⁺–) cm^{-1}.

Anal. Calcd for $C_{27}H_{28}BrNO_4 \cdot HCl$: N, 2.52. Found: N, 2.41.

A suspension of 8.5 g of the hydrochloride in 10% ammonia was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 7.5 g of the isoquinoline **10a**, mp 115–117° (from methanol), $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (–C=N).

Anal. Calcd for $C_{27}H_{28}BrNO_4$: C, 63.58; H, 5.53; N, 2.75. Found: C, 63.34; H, 5.45; N, 3.05.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (**11a**).—A mixture of 7 g of **10a**, 10 ml of methyl iodide, and 50 ml of methanol was allowed to stand at room temperature. The pale yellowish precipitate was collected by filtration and recrystallized from methanol to give 9 g of **11a** as pale yellowish needles, mp 200–202°, $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{28}H_{31}BrINO_4$: C, 51.58; H, 4.79; N, 2.16. Found: C, 51.72; H, 4.55; N, 2.20.

7-Benzyloxy-1-(2-bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**12a**).—To a stirred solution of 8 g of **11a** in 150 ml of methanol was added in small portions 3 g of sodium borohydride. After the stirring had been continued for 1 hr, the solvent was evaporated. The resulting residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 6 g of **12a** as a pale brownish oil, $\nu_{max}^{CHCl_3}$ 2780 cm^{-1} (NCH_3). The methiodide prepared as usual was recrystallized from methanol to afford colorless needles, mp 165–166°.

Anal. Calcd for $C_{29}H_{35}BrINO_4$: C, 52.04; H, 5.13; N, 2.09. Found: C, 51.90; H, 5.10; N, 2.38.

1-(2-Bromo-4,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13a**).—A mixture of 5 g of the preceding isoquinoline **12a**, 50 ml of concentrated hydrochloric acid, and 50 ml of ethanol was refluxed for 2 hr. After removal of the solvent, the resulting residue was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 3.8 g of **13a** as a pale brownish oil, $\nu_{max}^{CHCl_3}$ 3490 (OH) and 2730 cm^{-1} (NCH_3). The methiodide prepared as usual gave colorless needles, mp 230–233°.

Anal. Calcd for $C_{22}H_{29}BrINO_4$: C, 45.71; H, 4.88; N, 2.42. Found: C, 45.86; H, 5.15; N, 2.51.

Photolysis of 13a.—A stirred mixture of 2 g of the phenolic isoquinoline **13a**, 1 g of sodium hydroxide, 500 ml of ethanol, and 500 ml of water was irradiated using a 450-W Hanovia mercury lamp with a Pyrex filter under water cooling for 7 hr. The solvent was evaporated and extracted with chloroform after the addition of an excess of crystalline ammonium chloride. The extract was washed with water, dried over sodium sulfate, and evaporated to leave 1.5 g of a brownish oil. This was chromatographed on silica gel (45 g). After the chloroform fractions (fractions 1–9, each fraction 90 ml) had been discarded, the elution with methanol–chloroform (1:99) (fractions 10–16) gave the phenolic isoquinoline **13a**, and the elution with methanol–chloroform (2:98) (fractions 17–19) afforded 105 mg of a mixture of the dienone **14** and homoaporphine **15**. Finally, the elution with the same solvent (fractions 20–27) as above afforded 200 mg of **15** as colorless needles: mp 195–196° (from methanol–ether); nmr ($CDCl_3$) τ 2.92, 3.27, 3.43 (3 H, each singlet, aromatic protons), 6.12 (6 H, singlet, $2OCH_3$), 6.16 (3 H, singlet, OCH_3), 7.63 (3 H, singlet, NCH_3); mass spectrum *m/e* 355 (M^+), 338 ($M^+ - OH$).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.75; H, 7.30; N, 3.93.

The former mixture chromatographed on 5 g of neutral alumina using benzene–chloroform (8:2) gave 20 mg of the dienone **14** as a colorless oil, whose spectroscopic data were identical with those of an authentic specimen.[10]

N-(**4-Benzyloxy-3-methoxyphenethyl**)-**3**-(**2-bromo-3,4,5-trimethoxyphenyl**)**propionamide** (**9b**).—A mixture of 10 g of 4-benzyloxy-3-methoxyphenethylamine and 12.4 g of 2-bromo-3,4,5-trimethoxyphenylacetic acid was heated at 140° for 20 min and then at 180° for 1.5 hr. The mixture was extracted with benzene. The extract was washed with water, dried over sodium sulfate, and evaporated. The residual oil was recrystallized from benzene–hexane to give 18 g of **9b** as colorless needles: mp 104.5–106.5°; $\nu_{max}^{CHCl_3}$ 3400 (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) τ 6.20–6.03 (12 H, broad singlet, $4OCH_3$), 4.89 (2 H, singlet, OCH_2Ph), 2.74 (1 H, broad singlet, NHCO), 3.55, 3.12 (4 H, multiplet, aromatic protons), 2.74–2.46 (5 H, broad singlet, aromatic protons).

Anal. Calcd for $C_{28}H_{32}BrNO_6$: C, 60.22; H, 5.78; N, 2.51. Found: C, 60.22; H, 5.60; N, 2.55.

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**10b**).—A mixture of 12 g of the preceding amide **9b**, 12 ml of phosphoryl chloride, and 100 ml of dry chloroform was refluxed for 2 hr. The solvent was evaporated and the residual oil was washed with hexane. Recrystallization of the crude hydrochloride from methanol–ether afforded 8 g of **10b** as colorless needles, mp 184–185°, $\nu_{max}^{CHCl_3}$ 1650 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{28}H_{30}BrNO_5 \cdot HCl$: C, 58.29; H, 5.42; N, 2.43. Found: C, 58.01; H, 5.58; N, 2.61.

A solution of 7 g of the preceding hydrochloride in 50 ml of chloroform was washed with 10% ammonia and water. The solvent was evaporated to give 6 g of the isoquinoline **10b** as a pale brownish oil: $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (>C=N–); nmr ($CDCl_3$) τ 6.53–6.86 (12 H, $4OCH_3$); 4.89 (2 H, singlet, OCH_2Ph), 3.38 (2 H, singlet, aromatic protons), 2.88–2.42 (6 H, multiplet, aromatic protons).

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (**11b**).—A mixture of 6 g of **10b**, 5 ml of methyl iodide, and 50 ml of methanol was left at room temperature. The yellow precipitate was filtered and recrystallized from methanol–ether to give 4 g of **11b** as pale yellowish needles, mp 193–195°, $\nu_{max}^{CHCl_3}$ 1628 cm^{-1} (>C=N⁺–).

Anal. Calcd for $C_{29}H_{33}BrINO_5$: C, 51.05; H, 4.87; N, 2.05. Found: C, 51.19; H, 4.92; N, 2.13.

7-Benzyloxy-1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**12b**).—To a cooled mixture of 3.5 g of **11b**, 80 ml of methanol, 20 ml of chloroform, and 1 drop of water was added in portions 1.5 g of sodium borohydride under stirring. The mixture was stirred for a further 1 hr and then refluxed for 0.5 hr. The solvent was evaporated, and the remaining residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over

(15) T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. C*, 1923 (1971).

(16) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *ibid.*, 2030 (1969), and references cited therein.

(17) Melting points are not corrected. Infrared spectra were measured with a type EPI-3 Hitachi recording spectrometer, and nmr spectra were taken with a Hitachi R-20 spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

potassium carbonate, and evaporated to give 2.6 g of **12b** as a colorless oil, bp 205–210° (bath temperature) (0.05 mm), after purification by distillation, $\nu_{max}^{CHCl_3}$ 2780 cm^{-1} (NCH_3).

Anal. Calcd for $C_{29}H_{34}BrNO_5$: C, 62.59; H, 6.16; N, 2.52. Found: C, 62.33; H, 6.13; N, 2.40.

1-(2-Bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (13b).—A mixture of 2.6 g of the preceding isoquinoline (**12b**), 30 ml of concentrated hydrochloric acid, and 30 ml of ethanol was refluxed for 4 hr. The solvent was evaporated, and the remaining residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water and dried over potassium carbonate. Evaporation of the solvent afforded 1.8 g of **13b** as a pale brownish oil, which was difficult to crystallize and therefore used in the following reaction without purification, $\nu_{max}^{CHCl_3}$ 3510 (OH) and 2730 cm^{-1} (NCH_3).

Photolysis of 13b.—A stirred mixture of 1.8 g of the phenolic isoquinoline **13b**, 0.5 g of sodium hydroxide, 250 ml of ethanol, and 750 ml of water was irradiated using a 450-W Hanovia mercury lamp with a Pyrex filter under water cooling for 7 hr. The mixture was extracted with chloroform after the addition of 6 g of ammonium chloride. The extract was washed with water, dried over potassium carbonate, and evaporated to leave 1.6 g of a brownish oil which was chromatographed on silica gel (50 g). Removal of the eluate with 1% methanol–chloroform gave a dienone fraction (440 mg), which was further rechromatographed on silica gel (10 g). Evaporation of the eluate with chloroform–methanol (99:1) afforded 210 mg of the dienone fraction, which was again rechromatographed on 10 g of neutral alumina. The elution with benzene–chloroform (19:1) gave 50.5 mg of *O*-methylandrocymbine (**8**). Recrystallization from ether–hexane afforded colorless prisms, mp 154–156.6°,[18] the spectroscopic data of which were identical with those of an authentic specimen.[7]

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55, H, 7.06. Found: C, 68.68; H, 7.24.

Removal of the subsequent elution after collection of the dienone fraction afforded 40 mg of kreisigine (**17**): mp 187–188° (from ethanol) (lit.[15] mp 187–188°); $\nu_{max}^{CHCl_3}$ 3500 cm^{-1} (OH); λ_{max}^{MeOH} 258 and 291 nm (log ϵ 4.02 and 3.82); nmr ($CDCl_3$) 7.60 (3 H, singlet, NCH_3), 6.38 (3 H, singlet, OCH_3), 6.12 (9 H, singlet, $3OCH_3$), 3.41 (1 H, singlet, aromatic proton), 3.38 (1 H, singlet, aromatic proton); mass spectrum *m/e* 385 (M^+), 368 ($M^+ - 17$). The spectral data were identical with those of an authentic sample.[15]

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.68. Found: C, 68.35; H, 7.28; N, 3.62.

Registry No.—**8**, 31735-12-3; **9a**, 31735-13-4; **9b**, 31790-84-8; **10a**, 31735-15-6; **10a** HCl, 31735-14-5; **10b**, 31790-85-9; **10b** HCl, 31735-16-7; **11a**, 31790-87-1; **11b**, 31735-17-8; **12a** methiodide, 31735-18-9; **12b**, 31735-19-0; **13a** methiodide, 31790-86-0; **13b**, 31735-20-3; **15**, 31735-21-4; **17**, 31735-22-5.

Acknowledgments.—We thank Miss Y. Tadano for nmr determination, Miss A. Kawakami and Miss C. Yoshida for microanalysis, and T. Ohuchi for mass spectral measurements.

(18) In a previous paper,[7] we reported *O*-methylandrocymbine to be an oil, but, after being allowed to stand for a long time, it crystallized.

Bufadienolides. 14. Synthesis of Bufotalien, 15α-Hydroxybufalin, and Resibufogenin[1]

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Conversion of 14-dehydrobufalin (**2a**) to bufotalien (**4a**) was accomplished. Peracid oxidation of 3β-acetoxy-14-dehydrobufalin (**2b**) was employed to obtain 14α,15α-epoxide **5b**. Sulfuric acid catalyzed opening of epoxide **5b** was used to complete a route to 15α-hydroxybufalin (**6b**). Treatment of diol **6b** with methanesulfonyl chloride led to a new synthesis of 3β-acetoxyresibufogenin (**3b**). Conversion of 14-dehydrobufalin to the halohydrins represented by structures **6d–g** followed by treatment with basic alumina or hot pyridine afforded resibufogenin in good yield. The epoxide formation catalyzed by alumina was also shown to yield 14α-artebufogenin (**8b**).

Interest in the chemistry and physiological action of amphibian venom constituents, for example, from the family Bufonidae, continues to increase.[2] We recently summarized a total synthesis of bufalin (**1a**) and resibufogenin (**3a**) employing 14-dehydrobufalin (**2a**) as relay.[3] The study was subsequently expanded to preparation of bufotalien[4] and to establish alternative routes from 14-dehydrobufalin to resibufogenin. A summary of these new conversions now follows.

To verify the structure of bufotalin[4] it became necessary to extend the total synthesis of 14-dehydrobufalin[3,5] to bufotalien (**4a**). An extensive attempt to convert olefin **2b** to diene **4b** by means of sulfur dehydrogenation proved impractical. However, mild treatment of olefin **2b** with *N*-bromosuccinimide followed by pyridine-catalyzed dehydrohalogenation did afford 3β-acetoxybufotalien (**4b**). Selective saponification of acetate **4b** to bufotalien (**4a**) was achieved using alumina. The synthetic diene (**4a**) was identical with a specimen prepared by acid-catalyzed dehydration of bufotalin (**1d**) essentially as previously reported.[6]

As part of the bufotalin investigation we were led to restudy the *m*-chloroperbenzoic acid oxidation of 14-dehydrobufalin.[3] When the oxidation was carried out with more recently purchased samples of *m*-chloroperbenzoic acid, formation of 14α,15α-epoxide **5** was obtained in high yield. The oxidation was repeated several times each with alcohol **2a** and acetate **2b** in chloroform or benzene with the same result (**5**). Unlike the initial study[3] no isolatable amounts of β-epoxide **3** were detected. Thus it became important to more firmly establish tranformation of 14-dehydrobufalin (**2a**) to resibufogenin (**3a**). Toward this

(1) For paper 13 (Steroids and Related Natural Products. 67), refer to G. R. Pettit and J. Dias, *J. Org. Chem.*, **36**, 3207 (1971).

(2) For example, see G. Habermehl, *Naturwissenschaften*, **56**, 615 (1969); Y. Kamano, *Kagaku No Ryoiki*, **24** (4), 57 (1970); Y. Kamano, *ibid.*, **24** (5), 27 (1970); G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970); and W. Haede, W. Fritsch, K. Radscheit, U. Stache, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **741**, 92 (1970).

(3) G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **35**, 2895 (1970).

(4) The bufotalien synthesis reported herein in detail was summarized in a preliminary communication: G. R. Pettit, P. Brown, F. Bruschweiler, and L. E. Houghton, *Chem. Commun.*, 1566 (1970).

(5) F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969).

(6) K. Meyer, *Helv. Chim. Acta*, **32**, 1993 (1949); H. Wieland, J. Hesse, and R. Huttel, *Justus Liebigs Ann. Chem.*, **524**, 203 (1936); H. Kondo and S. Ikawa, *J. Pharm. Soc. Jap.*, **53**, 23 (1933); *Chem. Abstr.*, **27**, 1887 (1933).