the following deuterium distribution data: **15** (M^+) 20 d_4, 77 d_5, 0 d_6, 4 d_7 (average, 4.96); **16** (M^+), 2 d_0, 5 d_1, 6 d_2, 18 d_3, 61 d_4, 7 d_5 (average, 3.50).

F. Brief Deuteriotrifluoroacetolysis.—A solution of tosylate **3c** (200 mg, 0.43 mmol) in 25 ml of buffered deuteriotrifluoroacetic acid was allowed to stand at room temperature for 5 min, then quenched quickly with 5% ethanolic potassium hydroxide. The alcohol solution was concentrated, water was added, and the product was isolated by extraction with hexane. Crystallization from hexane afforded 70 mg (52%) of tertiary hydroxy ester **2a**. The nmr spectrum of this material lacked the methyl peak at τ 8.69. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 3 d_1, 17 d_2, 44 d_3, 38 d_4 (average, 3.25).

Solvolysis of Tosylate 11c. A. Acetolysis.—Tosylate **11c** was subjected to acetolysis as above with **3c** for 25 hr at 85°. Evaporation of the acetic acid and isolation by hexane extraction afforded mainly methyl Δ^{15}-*ent*-atisen-19-oate (**12**) according to nmr analysis on the crude product.

B. Formolysis.—Tosylate **11c** (36 mg) was subjected to formolysis as described above with **3c** for 20 hr at room temperature. The nmr spectrum of the product obtained after isolation procedure A was identical with that of **14a** (methyl *ent*-16-hydroxyatisan-19-oate).[13]

C. Trifluoroacetolysis.—A 900-mg (1.8 mmol) portion of **11c** was added to 40 ml of buffered trifluoroacetic acid. After 5 min at room temperature, a 4-ml aliquot of the solution was removed and subjected to isolation procedure B. On crystallization of the residue from hexane, alcohol **14a** was obtained (by melting point, glpc, analysis, nmr, and ir spectral comparison).[13] After 20 hr at room temperature, a second 4-ml aliquot was removed and treated according to procedure B. Glpc and nmr spectral analyses on the product indicated the presence of **11b** (~80%) along with small amounts of **3b** and **4b**. The reaction was allowed to continue for 96 hr at room temperature and an additional 24 hr at 42°. Isolation according to isolation procedure B and purification by chromatography as described above (part C, formolysis of **3c**) gave **11b** (245 mg, 45%), **3b** (65 mg, 12%), and **4b** (25 mg, 5%). Acetates **11b** and **3b** were identified by melting point glpc and nmr and ir comparisons, acetate **4b** by glpc and nmr comparisons.

Deuteriotrifluoroacetolysis of Hydroxy Ester 11a.—A solution of **11a** in 20 ml of buffered deuteriotrifluoroacetic acid was allowed to stand for 15 min at room temperature. The product was then separated by isolation procedure A. Crystallization of the residue from hexane afforded labeled hydroxy ester **14a** (210 mg, 86%). The nmr spectrum was identical with that of unlabeled **14a**[13] except for the complete absence of the C-17 methyl signal at τ 8.71. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 1 d_1, 3 d_2, 12 d_3, 33 d_4, 47 d_5, 1 d_6 (average, 4.18); (M − 18) 3 d_2, 10 d_3, 34 d_4, 51 d_5 (average, 4.52).

The labeled hydroxy ester **14a** (190 mg, 0.57 mmol) was dehydrated with thionyl chloride (1 ml) in 20 ml of methylene chloride and 8 ml of pyridine and the resulting mixture of atiserene esters **12** and **13** was separated chromatographically on 18% silver nitrate–silica gel as previously described.[13] In the nmr spectrum of the labeled endocyclic isomer **12** (80 mg, 44%, mp 90–91°), the vinyl methyl group (τ 8.28) was reduced to $<1/4$ of the original intensity and the vinyl proton (τ 4.42) to ~0.1 H. Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 5 d_0, 4 d_1, 9 d_2, 28 d_3, 51 d_4 4 d_5 (average 3.35). The nmr spectrum for the exocyclic isomer **13** (40 mg, 21%, mp 125.5–127°) showed a substantially reduced intensity for the vinyl protons (τ 5.3–5.4) and the allylic methylene group (τ 8.04). Analysis of the mass spectrum gave the following deuterium distribution: (M^+) 7 d_0, 3 d_1, 9 d_2, 33 d_3, 55 d_4 (average 3.48).

Deuteriotrifluoroacetolysis of Other Diterpene Substrates.—In each of the following experiments, the substrate was subjected to solvolysis in buffered deuteriotrifluoroacetic acid (10–25 ml) for 20–21 hr at room temperature. After work-up by isolation procedure B, acetate **11b** was isolated by column chromatography and/or crystallization from methanol. The deuterium distribution data were obtained from the mass spectrum of **11b** after correction for ^{13}C natural abundance. The yields were estimated from glpc traces.

A.—Methyl *ent*-16α-hydroxykauran-19-oate (**2a**, 470 mg) in 55 ml of buffered deuteriotrifluoroacetic acid gave, after purification by column chromatography (see part C, formolysis of **3c**), **11b** (46%): (M − 60) 4 d_3, 23 d_4, 69 d_5, 5 d_6 (average, 4.78).

B.—Methyl Δ^{16}-*ent*-kauren-19-oate (**5**, 110 mg) in 55 ml of the labeled solvent gave, after purification by column chromatography, **11b** (45%): (M − 60), 11 d_4, 85 d_5, 5 d_6 (average, 4.95).

C.—Methyl Δ^{15}-*ent*-atisen-19-oate (**12**, 50 mg)[13] gave **11b** in ~80% yield: (M − 60) 11 d_4, 85 d_5, 4 d_6 (average 4.93).

D.—Methyl Δ^{16}-*ent*-atisen-19-oate (**13**, 56 gm)[13] gave **11b** in ~80% yield: (M − 60) 1 d_3, 12 d_4, 83 d_5, 4 d_6 (average 4.90).

E.—Methyl *ent*-13α,16-cycloatisan-19-oate (**9**, 24 mg) gave **11b** in ~80% yield: (M − 60) 4 d_4, 18 d_5, 76 d_6, 3 d_7 (average, 5.78); (M − 75) 20 d_5, 80 d_6, 1 d_7 (average, 5.85).

Registry No.—**1**, 21682-55-3; **2a**, 22376-08-5; **3c**, 31819-20-2; **5**, 5524-25-4; **6**, 18671-79-9; **7**, 14699-35-5; **8**, 21682-50-8; **11c**, 31819-24-6; **26**, 30288-12-1; *ent*-13α,16-cycloatisan-19-ol, 31819-26-8.

Studies on the Syntheses of Heterocyclic Compounds. CDL. Total Synthesis of Androcymbine

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Photolysis of the diazonium salts **4** and **14** of 6,7-dimethoxy- (**3**) and 7-benzyloxy-6-methoxy-1-(2-amino-4-benzyloxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (**13**) gave *O*-benzylandrocymbine (**8**), which was debenzylated to afford (±)-androcymbine (**2**). Also the same reaction of a diazonium salt **19**, however, gave the abnormal product, homoproaporphine (**20**).

Androcymbine (**2**),[1] the principal member of a family of 1-phenethylisoquinoline alkaloids, has been biosynthesized from the diphenolic phenethylisoquinoline (**1**)[2] (Scheme I). Three synthetic methods have been developed for androcymbine-type compounds: the first by phenol oxidation,[3] the second by Pschorr reaction,[4] and the third by photolysis of diazonium salts.[5] Herein we wish to report the total synthesis of androcymbine by the photolysis of the diazonium salts **4** and **14** and the abnormal reaction during the photolysis of the phenolic diazonium salt **19**.

(1) J. Hrbek, Jr., and F. Šantavý, *Collect. Czech. Chem. Commun.*, **27**, 255 (1962); A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Commun.*, 228 (1965).

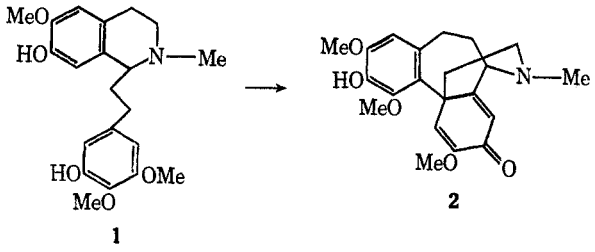
(2) A. C. Baker, A. R. Battersby, E. McDonald, R. Ramage, and J. H. Clements, *ibid.*, 36 (1967), and references cited therein.

(3) T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *ibid.*, 1605 (1968); *J. Chem. Soc. C*, 1295 (1969).

(4) T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Commun.*, 1001 (1968); *J. Chem. Soc. C*, 3084 (1968).

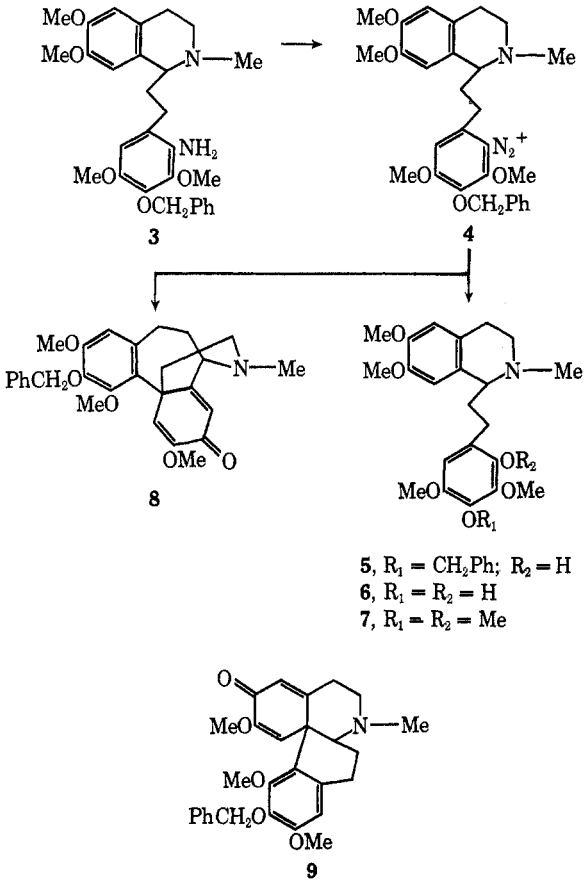
(5) T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Commun.*, 1157 (1970); *J. Chem. Soc. C*, 1792 (1971).

SCHEME I



Diazotization of the 2′-aminophenethylisoquinoline **3**[6] in the usual way, followed by photolysis with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10°, gave four compounds after separation by silica gel column chromatography (Scheme II).

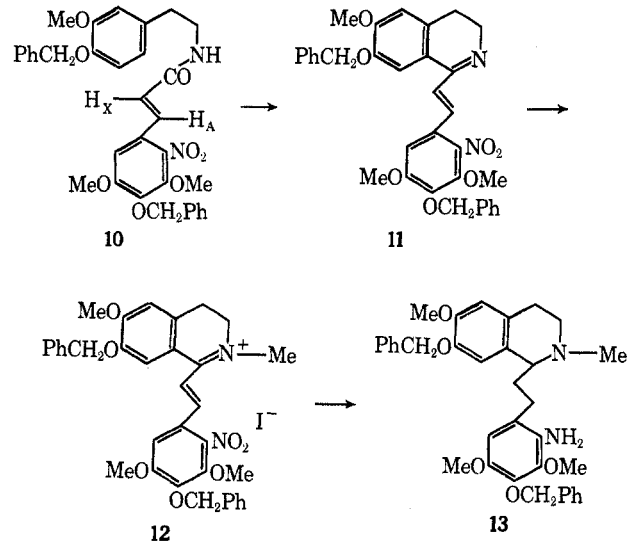
SCHEME II



The first compound in 0.5% yield was assigned as 4-benzyloxy-3,5-dimethoxybenzaldehyde by direct comparison with the authentic sample.[6] The second eluent afforded 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril in 1% yield; this was identical in all aspects with the authentic sample.[7] The third compound in 9.2% yield was assigned as 1-(4-benzyloxy-2-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**5**) by the following evidence. The infrared spectrum revealed this compound to be a phenolic isoquinoline and the ultraviolet spectrum showed this compound to be 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. The nmr spectrum revealed three aromatic protons with one *O*-benzyl, four *O*-methoxy, and one *N*-methyl resonances. Debenzylation of **5**, followed by O-methylation with diazomethane, gave hexamethoxyphenethylisoquinoline (**7**), which was identical with the authentic sample.[5] The fourth compound in 1.4% yield had the molecular formula $C_{28}H_{31}NO_5$ by mass spectrometry, and showed the typical cross-conjugated α-methoxycyclohexadienone system in infrared and ultraviolet spectra.[3-5] The nmr spectrum showed an *N*-methyl (τ 7.63), three *O*-methyls (6.4, 6.23, and 6.02), and the methylene of one benzyloxy group (5.05). Also two olefinic and one aromatic protons at τ 3.76, 3.73, and 3.26 were observed, each as singlets. According to the above data, the possible structure could be either the desired *O*-benzylandrocymbine (**8**) or **9**. However, structure **9** was ruled out by the following evidence.

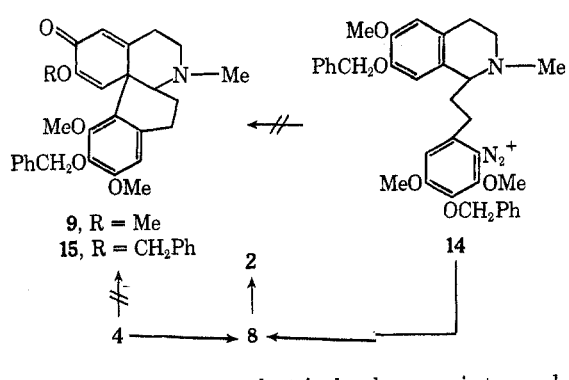
If the structure of the dienone were **9**, the products from the aminoisoquinoline **3** and **13** should be different. On the grounds of this consideration, we examined photolytic decomposition of the diazonium salt **14** derived from aminoisoquinoline **13**, which was synthesized as described in the Experimental Section and Scheme III.

SCHEME III



The diazotization of **13**, followed by photolysis of the diazonium salt **14** in a manner similar to the above, gave the same dienone **8** (Scheme IV).

SCHEME IV



Thus it was apparent that in both cases intramolecular reaction had occurred between the 2′ and 4a posi-

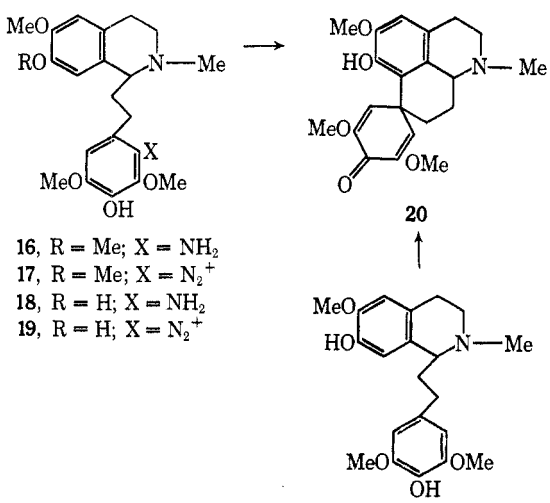
(6) T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. C.*, 1032 (1971).

(7) T. Kametani, M. Koizumi, and K. Fukumoto, *J. Pharm. Soc. Jap.*, **90**, 1331 (1970).

tions in the isoquinoline skeleton. Debenzylation of **8** gave (±)-androcymbine (**2**), an alkaloid from *Androcymbium melanthioides* var. *stricta*, the spectral data of which were superimposable upon those of natural androcymbine.[1]

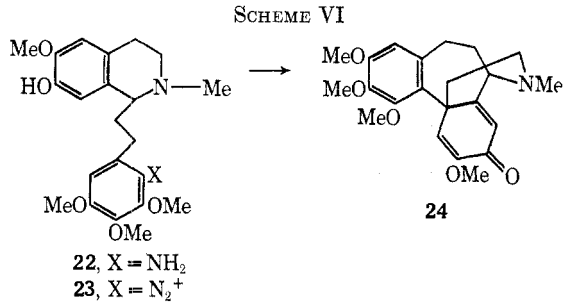
Moreover, in order to obtain androcymbine directly, the photolysis of the diazonium salts **17** and **19** was investigated. The irradiation of a diazonium salt **17**, obtained by the usual method from **16**, which was prepared from the 4′-benzyloxy derivative **3**, under the same conditions as above, gave only isocarbostyril. On the other hand, the diazotization of diphenolic aminoisoquinoline **18**, prepared from **13**, gave the diazonium salt **19**, which was photolyzed with a mercury lamp under the same conditions as above to give an unexpected compound, homoproaporphine **20**, as the main product. The spectra of the compound were superimposable upon those of an authentic sample of **20**,[8] prepared from a diphenolic isoquinoline **21** by phenolic oxidation (Scheme V).

SCHEME V



However, the photolysis of the diazonium salt **23** from a monophenolic aminoisoquinoline **22** afforded a normal product, *O*-methylandrocymbine **24**[9] (Scheme VI).

SCHEME VI



Therefore, we hypothesize that a phenolic hydroxy group on the phenethyl residue played an important role in this abnormal reaction. When the diazonium salt **19** was treated at 5–10° for 4 hr in dilute sulfuric acid without irradiation, no homoproaporphine **20** was obtained. Moreover, the photolysis of a diphenolic isoquinoline **21** and the presence of nitrous acid recovered the starting material **21**. Therefore, the homoproaporphine **20** would have been formed *via* the radical intermediates **25**, **26**, and **27** (Scheme VII).

Thus, we have accomplished the total synthesis of (±)-androcymbine and confirmed that its structure is **2** as suggested by Battersby.[1]

(8) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Commun.*, 878 (1967); T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

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

Experimental Section

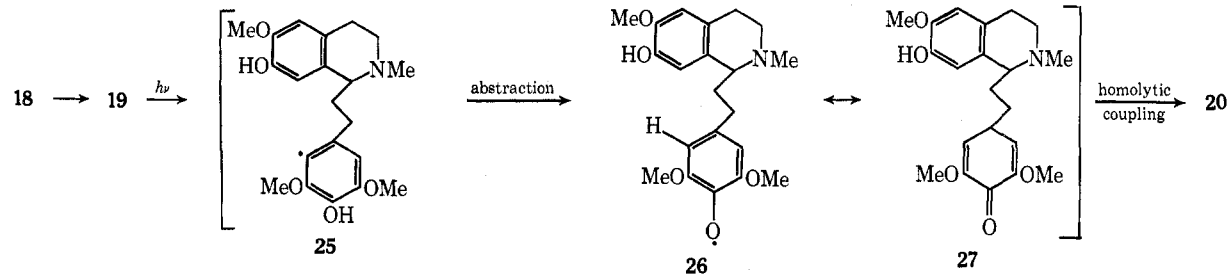
Melting points were determined on a Yanagimoto microapparatus (MP-S2) and are uncorrected. Infrared spectra were obtained on a Hitachi EPI-3 recording spectrophotometer in chloroform solution. Ultraviolet spectra were recorded on a Hitachi recording spectrophotometer (EPS-3) in methanol. Nuclear magnetic resonance spectra of deuteriochloroform solution containing tetramethylsilane ($\delta = 10\ \tau$) as internal standard were taken on a Hitachi R-20 spectrometer. Mass spectra were taken on a Hitachi RMU-7 spectrometer.

Photolysis of Diazonium Salt of 3.—To a stirred solution of 4.0 g (8.2 mmol) of aminoisoquinoline **3**[6] in 200 ml of 1 *N* sulfuric acid and 60 ml of acetic acid was added dropwise a solution of 700 mg (10.3 mmol) of sodium nitrite in 7 ml of water during 30 min at 3° and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 2 l. with water, the reaction mixture was irradiated with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10° for 4 hr. The reaction mixture was then made basic with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to afford 3.8 g of a dark brown gum, which was subjected to chromatography on 100 g of silica gel with chloroform (fractions 1–13, each 200 ml) and chloroform–methanol (99:1 v/v; fractions 14–36) as eluents inspecting with thin layer chromatography, infrared, and ultraviolet spectra. Fraction 2 gave 10 mg (0.5%) of 4-benzyloxy-3,5-dimethoxybenzaldehyde as a pale yellow glass. The thin layer chromatography and infrared spectrum of this product were identical with those of an authentic sample.[6] Fraction 7 gave 18 mg (1%) of 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril as colorless plates, mp 124–125° (lit.[7] 124–125°) (from ethyl acetate), infrared C=O at 6.1 μ (s), which was identical with the authentic sample.[7] Fractions 16–23 gave 370 mg (9.2%) of 1-(4-benzyloxy-2-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (**5**) as a viscous syrup: infrared hydroxy group at 2.86 μ (s); ultraviolet 283 nm; nmr τ 7.62 (3, s, NCH_3), 6.31 (9, s, 3 OCH_3), 6.22 (3, s, OCH_3), 5.11 (2, s, benzyl CH_2), 3.77 (1, s, 6′-HO), 3.65 (2, s, 5 H and 8 H), 3.76 (5, s, benzyl C_6H_5). Fractions 28–34 gave 210 mg of the crude compound **8** which was rechromatographed on 15 g of silica gel using chloroform containing 1% methanol as an eluent to give 105 mg of a pale brown syrup. Further purification was achieved through chromatography on 15 g of alumina using benzene containing 30% chloroform as an eluent. Evaporation of the appropriate fractions gave 50 mg (1.4%) of (±)-*O*-benzylandrocymbine (**8**) as a pale yellow viscous syrup: infrared cyclohexadienone system at 6.02 (s), 6.11 (s), and 6.20 μ (s); ultraviolet 237 and 281 nm (log ϵ 4.31 and 3.70); nmr spectrum τ 7.63 (3, s, NCH_3), 6.4 (3, s, OCH_3), 6.23 (3, s, OCH_3), 6.02 (3, s, OCH_3), 5.05 (2, s, benzyl CH_2), 3.76, 3.73, 3.26 (3, each s, an aromatic and two olefinic protons); mass spectum *m/e* 461 (M^+), 370 ($M^+ - 91$). Recrystallization of the methiodide of **8** from methanol–ether gave colorless needles, mp 251–253°.

Anal. Calcd for $C_{28}H_{31}NO_5 \cdot CH_3I$: C, 57.72; H, 5.68. Found: C, 57.68; H, 5.45.

***N*-(4-Benzyloxy-3-methoxyphenethyl)-4-benzyloxy-3,5-dimethoxy-2-nitrocinnamide (10).**—A solution of 32 g (85 mmol) of 4-benzyloxy-3,5-dimethoxy-2-nitrocinnamoyl chloride [prepared from 31 g (86.5 mmol) of the corresponding carboxylic acid and 25 g of phosphorus pentachloride in 250 ml of chloroform] was added dropwise to a solution of 30 g (115 mmol) of 4-benzyloxy-3-methoxyphenethylamine in 150 ml of 5% sodium hydroxide solution with stirring at 20°. After the stirring had been continued for 3 hr, the organic layer was separated, washed with 10% hydrochloric acid and water, dried over sodium sulfate,

SCHEME VII



and evaporated to give a residue, to which was added 10 ml of methanol. The separated crystals were collected by filtration, and recrystallization from methanol gave 46 g (90%) of the cinnamide **10** as yellow prisms: mp 152–153°; infrared amide NH at 2.94 (m), amide C=O at 6.00 (s), C=C at 6.13 μ (m); nmr spectrum τ 6.16 (6, s, 2OCH$_3$), 6.09 (3, s, OCH$_3$), 4.98 (2, s, benzyl CH$_2$), 4.92 (2, s, benzyl CH$_2$), 3.76 (1, d, J = 16 Hz, H$_X$), 2.64 (1, d, J = 16 Hz, H$_A$).

Anal. Calcd for $C_{34}H_{34}N_2O_8 \cdot 0.5\ H_2O$: C, 67.21; H, 5.81; N, 4.61. Found: C, 67.50; H, 5.93; N, 4.76.

7-Benzyloxy-1-[(4-benzyloxy-3,5-dimethoxy-2-nitrophenyl)-vinyl]-3,4-dihydro-6-methoxyisoquinoline (11).—A mixture of 15 g (25 mmol) of the amide **10**, 15 ml of phosphoryl chloride, and 150 ml of dry chloroform was heated under reflux for 45 min. An excess of hexane was added to the reaction mixture and the yellow precipitate, which was collected by filtration, was washed with hexane. After it had been dissolved in chloroform, the resultant solution was poured into cooled ammonia with stirring. The solvent layer was separated, washed with water, dried over sodium sulfate, and evaporated to give 10 g (69%) of **11** as a yellow syrup: infrared C=N at 6.12 (m), C=C at 6.17 μ (m); nmr spectrum τ 6.18 (6, s, 2OCH$_3$), 6.10 (3 H, s, OCH$_3$), 4.97 (2, s, benzyl CH$_2$), 4.98 (2, s, benzyl CH$_2$). Recrystallization of the hydrochloride from methanol gave pale yellow needles, mp 184–185°.

Anal. Calcd for $C_{34}H_{32}N_2O_7 \cdot HCl$: C, 66.18; H, 5.39; N, 4.54. Found: C, 66.48; H, 5.44; N, 4.41.

7-Benzyloxy-1-[(4-benzyloxy-3,5-dimethoxy-2-nitrophenyl)-vinyl]-3,4-dihydro-6-methoxyisoquinoline Methiodide (12).—A mixture of 10 g (17 mmol) of the 3,4-dihydroisoquinoline **11** and 20 ml (320 mmol) of methyl iodide was allowed to stand at room temperature for 12 hr, and the excess of methyl iodide was distilled off to leave 11 g (87%) of methiodide **12** as yellow crystals, the recrystallization of which from methanol–ether gave yellow needles, mp 110–112°.

Anal. Calcd for $C_{34}H_{32}N_2O_7 \cdot CH_3I$: C, 58.18; H, 4.88; N, 3.88. Found: C, 58.31; H, 4.97; N, 3.68.

1-(2-Amino-4-benzyloxy-3,5-dimethoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (13).—Within 1.5 hr at a temperature below 5°, 60 g (917 mg-atoms) of zinc powder was added in small portions to a stirred mixture of 11 g (15 mmol) of the above methiodide (**12**), 250 ml of concentrated hydrochloric acid, and 250 ml of glacial acetic acid. The stirring was continued at the same temperature for 6 hr. After removal of zinc by filtration, the filtrate was made basic with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and distilled to leave 8 g of the aminoisoquinoline, which was hydrogenated with hydrogen on 400 mg of Adams catalyst in 600 ml of methanol to give 7 g (82%) of **13** as a pale brown viscous syrup: nmr spectrum τ 7.59 (3, s, NCH$_3$), 6.28 (3, s, OCH$_3$), 6.19 (6 H, s, 2OCH$_3$), 5.01 (2, s, benzyl CH$_2$), 4.95 (2, s, benzyl CH$_2$), 3.68 (1, s, 6′ H), 3.47 (2, s, 5 H and 8 H), 2.71 (5, s, benzyl C$_6$H$_5$), 2.68 (5, s, benzyl C$_6$H$_5$). This was used because of difficulty in crystallization.

Photolysis of Diazonium Salt of 13.—To a stirred solution of 2.2 g (3.9 mmol) of aminoisoquinoline **13** in 100 ml of 1 *N* sulfuric acid was added dropwise a solution of 280 mg (4 mmol) of sodium nitrite in 3 ml of water at 3° during 30 min. The stirring was continued at 5° for 1 hr. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 1 l. with water, the reaction mixture was irradiated with a Hanovia 450-W mercury lamp using a Pyrex filter at 5–10° for 4 hr. The reaction mixture was treated in the same manner as in the case of **3**, giving the following substances: 13 mg (1.2%) of 7-benzyloxy-3,4-dihydro-6-methoxy-2-methylisocarbostyril as a pale brownish viscous syrup, infrared C=O at 6.11 μ (s), which was identical with the authentic sample,[5] and 10 mg (0.6%) of *O*-benzylandrocymbine (**8**) as a pale yellow viscous syrup, which was identical with the authentic sample described before.

(±)-Androcymbine (2).—A mixture of 60 mg (0.12 mmol) of *O*-benzylandrocymbine (**8**), 6 ml of 48% hydrobromic acid, and 18 ml of methanol was heated at 55° on a water bath for 45 min. After evaporation of the solvent *in vacuo*, the residue was treated with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 53 mg of a pale brown viscous syrup, which was purified by preparative thick layer chromatography on silica gel in chloroform–methanol (10:1 v/v) to give 3 mg (6.2%) of (±)-androcymbine (**2**) as a pale yellow viscous syrup together with 12 mg of the starting material **8**. Infrared, ultraviolet, and nmr spectra of the former compound (**2**) were identical with those of natural androcymbine: infrared hydroxy group at 2.86 (s), cyclohexadienone system at 6.02 (s), 6.12 (s), and 6.20 μ (s); ultraviolet 240 and 279 nm (log ϵ 4.18 and 3.62); nmr spectrum τ 7.62 (3, s, NCH$_3$), 6.39 (3, s, OCH$_3$), 6.19 (3, s, OCH$_3$), 5.99 (3, s, OCH$_3$), 3.76 (1, s, aromatic proton), 3.76 and 3.23 (2, each s, olefinic protons); mass (*m/e*) calcd for $C_{21}H_{25}NO_5$, 371.173 (found, 371.171).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2,3,4,5-tetramethoxyphenethyl)-2-methylisoquinoline (7).—A mixture of 200 mg (0.4 mmol) of **5**, 4 ml of ethanol, and 4 ml of concentrated hydrochloric acid was heated on a water bath for 3 hr. Evaporation of the solvent gave a viscous syrup, the solution of which in water was made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 140 mg (87.5%) of the 1,2,3,4-tetrahydro-1-(2,4-dihydroxy-3,5-dimethoxyphenethyl)-6,7-dimethoxy-2-methylisoquinoline (**6**) as a pale brown viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.57 (3, s, NCH$_3$), 6.21 (6, s, 2OCH$_3$), 6.15 (3 H, s, OCH$_3$), 6.11 (3 H, s, OCH$_3$), 3.60 (1, s, 6′ H), 3.43 (1, s, 5 H), 3.40 (1, s, 8 H). To a solution of 140 mg (0.35 mmol) of the above dihydroxyisoquinoline (**6**) in 4 ml of methanol was added an excess of diazomethane [prepared from *p*-toluenesulfonyl-*N*-methyl-*N*-nitrosamide (5 g)] and the mixture was allowed to stand at room temperature for 48 hr. The excess diazomethane and solvents were distilled off and the residue was distilled *in vacuo* to give 70 mg (47%) of **7** as a viscous syrup, bp 250–255° (0.5 mm), which was identical with an authentic sample.[5]

1-(2-Amino-4-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (16).—A mixture of 2 g (4.1 mmol) of benzylisoquinoline (**3**), 40 ml of ethanol, and 40 ml of concentrated hydrochloric acid was heated on a water bath for 3 hr. Evaporation of the solvent gave a viscous syrup, the aqueous solution of which was made basic with 10% ammonia and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 1.2 g (78%) of **16** as a pale brown viscous syrup: infrared hydroxy group at 2.86 μ (s); nmr spectrum τ 7.69 (3, s, NCH$_3$), 6.23 (6, s, 2OCH$_3$), 6.19 (6, s, 2OCH$_3$), 3.69 (1, s, 6′ H), 3.52 (2, s, 5 H and 8 H). This was labile in air and therefore used without purification.

Photolysis of the Diazonium Salt of 16.—To a solution of 1.2 g (3 mmol) of phenolic isoquinoline **16** in 70 ml of 1 *N* sulfuric acid and 10 ml of acetic acid was added dropwise a solution of 208 mg (3 mmol) of sodium nitrite in 2 ml of water during 20 min at 3° and the stirring was continued for a further 1 hr at the same temperature. After decomposition of the excess of nitrous acid with urea, followed by dilution to a volume of 1 l. with

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.

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

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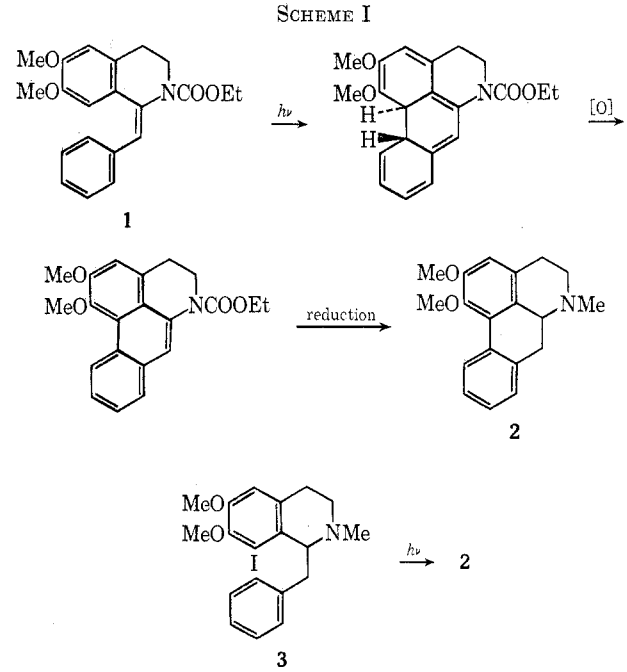
The total syntheses of (±)-*O*-methylandrocymbine (**8**) and (±)-kreysigine (**17**) by photolysis of 1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**13b**) are reported. The same reaction of the demethoxy analog **13a** to the homomorphinandienone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

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