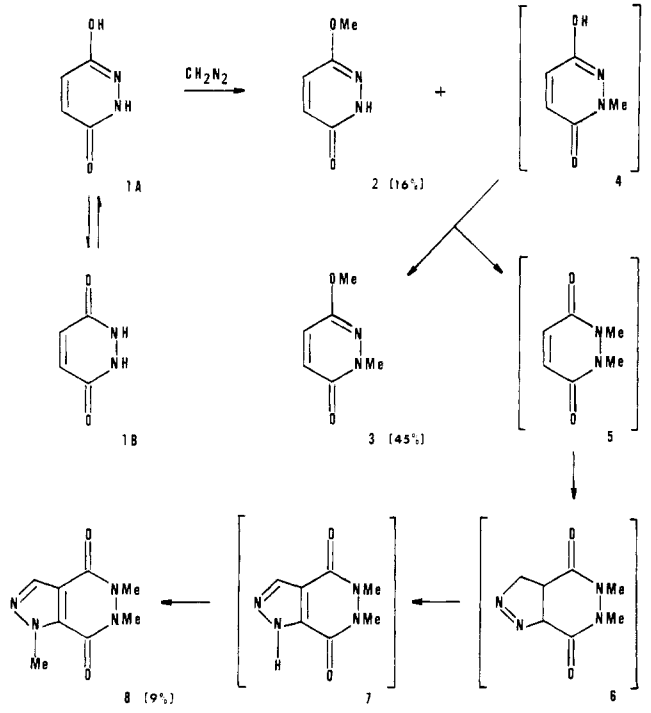
Scheme I



furnished substantial quantities of 8 and a trace of 5. However, the major product isolated proved to be the 2-methyl-6-methoxy derivative 3.

Some inferences from the foregoing experimental observations can be summarized as follows.

(a) In comparison to the N-methylated compound 4 the methoxy precursor 2 reacts very slowly with diazomethane. This suggests that initial nitrogen methylation is the preferred pathway to the 2-methyl-6-methoxy derivative 3.

(b) It appears that the *N*-pyrazolo derivative 8 is formed solely by reaction of diazomethane with the *N,N*-dimethyl intermediate 5. If so, the amount of 8 produced on reaction of the *N*-methyl derivative 4 with diazomethane can be taken as a measure of the intermediate *N,N*-dimethyl compound 5 involved. Thus, on the basis of product analysis, the preferred second stage of the reaction between maleic hydrazide and diazomethane proceeds by oxygen methylation. A possible explanation for this observation is that if as postulated for these types of reactions[7] a proton is transferred from compound 4 to diazomethane, reaction of methyldiazonium ion with nitrogen in the resultant pyridazinone anion may now be more sterically hindered by the presence of an adjacent *N*-methyl group.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hotstage microscope. NMR spectra were recorded on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. Infrared (IR) spectra were determined by using a Beckman IR-20A spectrophotometer. Mass spectra were determined on a Perkin-Elmer Hitachi mass spectrometer. A Tracor 222 gas chromatograph equipped with an electron-capture ^{63}Ni detector (with linearizer) and a nitrogen-specific detector were utilized for gas chromatography determinations. Thin-layer chromatograms (TLC) were run on glass plates coated with silica gel GF. Separated components were detected by UV fluorescence and iodine vapor.

Reaction of Maleic Hydrazide (1) with Diazomethane. A suspension of maleic hydrazide (1; 500 mg, 4.46 mmol) in diethyl ether (100 mL) was treated with an approximate fivefold excess of alcohol-free diazomethane[8] in diethyl ether. The mixture was stirred overnight at room temperature in the dark. The ether was then removed under vacuum and the residue purified by preparative TLC (ethyl acetate). Crystallization of the major component (R_f 0.53) from hexane gave 2-methyl-6-methoxy-3-(2*H*)-pyridazinone (3):284 mg (2.03 mmol); mp 64–65 °C (lit.[3] mp 64–66 °C); IR (Nujol) 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 6.89 (2 H, s, CH=CH), 3.83 (3 H, s, OCH_3), 3.65 (3 H, s, NCH_3); MS, *m/e* 140. Crystallization of a second component (R_f 0.44) from ethyl acetate gave 6-methoxy-3(2*H*)-pyridazinone (2):91 mg (0.72 mmol); mp 162–164 °C; IR (Nujol) 3175, 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.88 (1 H, s, NH), 6.95 (2 H, s, CH=CH), 3.82 (3 H, s, OCH_3); MS, *m/e* 126. Crystallization of a third component (R_f 0.27) from ethyl acetate afforded 1,2-dihydro-5,6-dihydro-1,5,6-trimethyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7-dione (8): 76 mg (0.39 mmol); mp 182–184 °C; IR (Nujol) 1660, 1550 cm^{-1}; NMR ($CDCl_3$) δ 8.06 (1 H, s, aromatic, N=CH), 4.30 (3 H, s, aromatic, NCH_3) 3.68 (3 H, s, $C(O)NCH_3$) 3.64 (3 H, s, $C(O)NCH_3$); MS, *m/e* 194. Repetition of the above reaction on compound 2 (35 mg) yielded compound 3 (4.6 mg) and starting material.

Reaction of 1,2-Dihydro-1,2-dimethyl-3,6-pyridazinedione (5) with Diazomethane. 1,2-Dihydro-1,2-dimethyl-3,6-pyridazinedione (5) was prepared from the reaction of maleic hydrazide (1) and dimethyl sulfate as described:[3] mp 136–137 °C (lit.[3] mp 135–136 °C); IR (Nujol) 1645, 1590 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (2 H, s, CH=CH), 3.68 (6 H, s, $C(O)NCH_3$); MS, *m/e* 140. It (70 mg, 0.5 mmol) was treated with an excess of ethereal diazomethane as described for maleic hydrazide. Preparative TLC clean-up furnished a compound (43 mg, 0.22 mmol) which had a melting point, mixture melting point, IR, and NMR identical with those of 8.

Reaction of 2-Methyl-6-hydroxy-3(2*H*)-pyridazinone (4) with Diazomethane. 2-Methyl-6-hydroxy-3(2*H*)-pyridazinone (4) was prepared from the reaction of maleic hydrazide (1) with dimethyl sulfate and dilute sodium hydroxide as described:[3] mp 210–212 °C (lit.[3] mp 210–211 °C); IR (Nujol) 1680, 1610, 1525 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ -10.95 (1 H, s, C=COH), 6.91 (2 H, s, CH=CH), 3.60 (3 H, s, NCH_3); MS, *m/e* 126. The compound (4; 100 mg, 0.79 mmol) was treated with an excess of ethereal diazomethane as described for maleic hydrazide. Preparative TLC furnished two major products. The first (45 mg, 0.33 mmol) had a melting point, mixture melting point, IR, and NMR identical with those of compound 3. The second compound (29 mg 0.15 mmol) had a melting point, mixture melting point, IR, and NMR identical with those of compound 8. Gas chromatographic analysis of the reaction mixture also indicated trace amounts (<2%) of compound 5.

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Registry No. 1, 123-33-1; 2, 1703-10-2; 3, 7154-81-6; 4, 5436-01-1; 5, 7685-97-4; 8, 83633-47-0; diazomethane, 334-88-3.

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Synthesis of (±)-*O*-Methylcryptaustoline Iodide

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Dibenzopyrrocoline derivatives obtruded into early laboratory attempts by Robinson[1] and Schöpf[2] to demonstrate the practicality of the biogenetic hypothesis for

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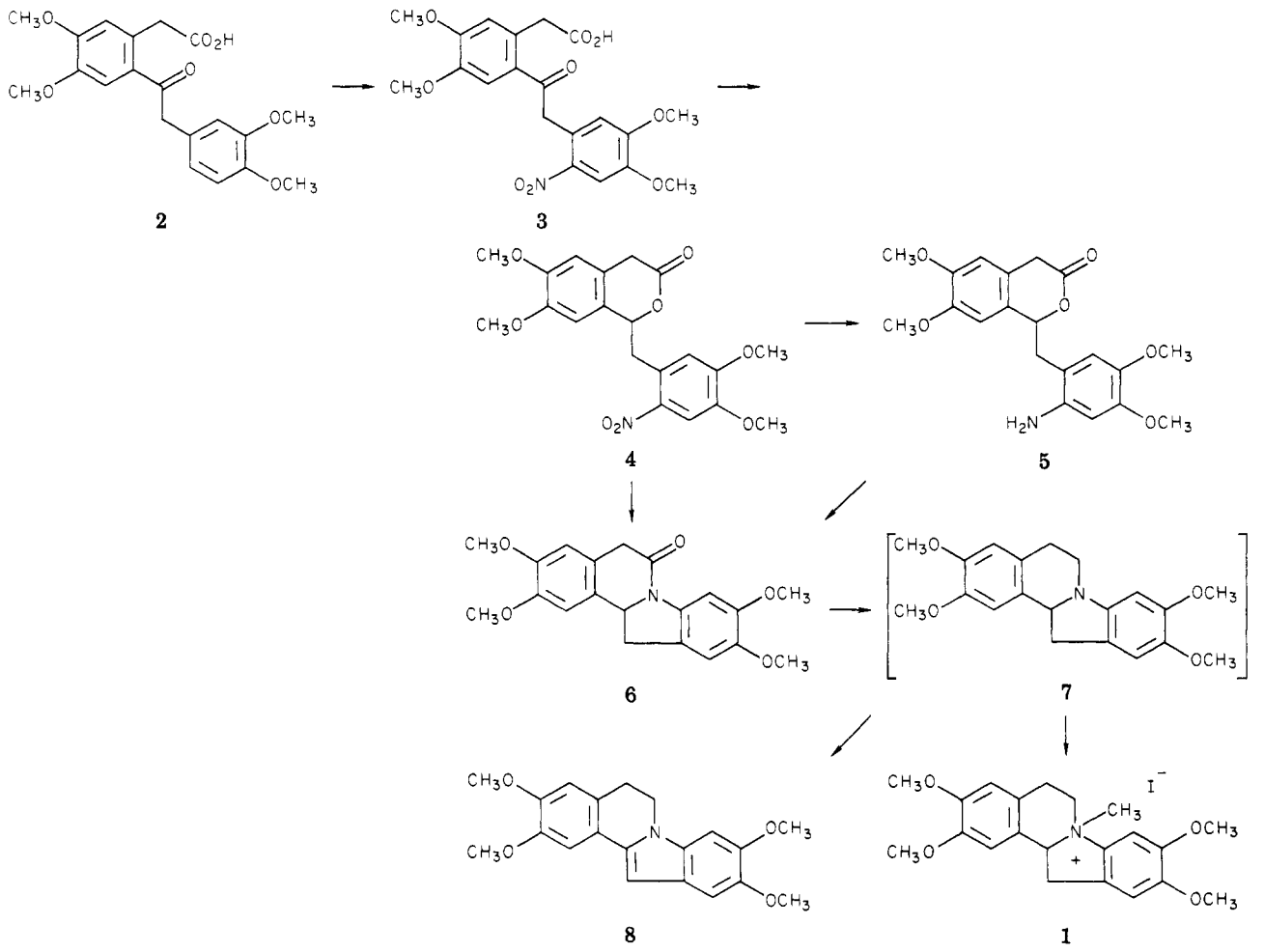
(2) Schöpf, C.; Thierfelder, K. *Justus Liebigs Ann. Chem.* **1921**, *498*, 22.

0022-3263/82/1947-5398$01.25/0

Scheme I



the formation of morphine or aporphine alkaloids by intramolecular oxidative coupling of laudanosoline. Later, two examples of this class of alkaloids, cryptaustoline and cryptowoline, were discovered in nature,[3] and several syntheses of both alkaloids and of *O*-methylcryptaustoline iodide (**1**) have been reported, principally through benzyne intermediates obtained from the appropriately substituted 1-benzyl-1,2,3,4-tetrahydroisoquinolines.[4] We report a new total synthesis of **1** by a route different from those previously recorded.

One theme of our research has been to devise new syntheses of a biogenetically related series of isoquinoline alkaloids from the keto acid **2**. The idea that **2** can be a common intermediate for the preparation of representative compounds of such structurally different types as the aporphine, morphine, isopavine, pavine, or dibenzopyrrocoline alkaloids is based on the fact that **2** possesses the requisite carbon skeleton and properly placed functional groups for conversion to members of each family. We have described new syntheses from **2** of laudanosine,[5] a spiro lactam,[6] and *O*-methylthalisopavine.[7] Other wokers have used **2** to prepare pontevedrine[8] and berberine analogues.[9]

A convenient five-step synthesis of *O*-methylcryptaustoline iodide (**1**) from **2** is outlined in Scheme I.

The keto acid **2** was nitrated in acetic acid. The nitro keto acid **3** was routinely obtained in 86% yield under the conditions described, but longer reaction times or excess nitric acid resulted in decreased yields. The position of the nitro group was originally predicted from the results of other electrophilic substitutions on **2**,[10] and the completed synthesis of **1** supports the assigned structure **3**. The nitro keto acid was reduced and cyclized to the nitro lactone **4** by sodium borohydride, followed by warm dilute acid. Further reduction of the nitro group in **4** was attempted by catalytic hydrogenation and by zinc in weakly acidic solution, but for the most part, the products were amorphous dark solids. Moreover, the nitro lactone **4** was only slightly soluble in most of the traditional solvents used for hydrogenation, and the quantities of **4** that could be reduced were severly limited. Trifluoroacetic acid (TFA) proved to be a powerful solvent for **4**, and from hydrogenation of **4** in TFA with Pd/C catalyst, small quantities of the lactam **6** were isolated, but the bulk of the crude product quickly decomposed to a dark resin. Reduction of **4** by zinc dust in MeOH–NH_4Cl likewise afforded a small amount of **6** as the principal isolable product. When the nitro lactone **4** was treated with iron dust in warm acetic acid, the product, obtained in 95% yield, proved to be the amino lactone **5**, and this compound, once isolated

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and purified, seemed quite stable. Attempts to convert the amino lactone **5** to the lactam **6** were unsuccessful in boiling dioxane or xylene or EtOH–$CHCl_3$, but **6** was obtained in about 50% yield from a solution of **5** in TFA–CH_2Cl_2 after 18 h. In subsequent trials, partial conversion of **5** to **6** was achieved in about the same yield with anhydrous magnesium sulfate in refluxing toluene for 24 h. The lactam **6** was reduced by BH_3–THF complex, and the hydrolyzed reaction mixture, in CH_2Cl_2 solution, was divided into two portions. Efforts to isolate the expected tertiary base **7** from one portion afforded only the dihydrodibenzopyrrocoline **8**, apparently formed by air-oxidation of **7** as reported by Robinson and Sugasawa.[1] The second portion of the reaction mixture was treated with methyl iodide to give crystalline *O*-methylcryptaustoline iodide (**1**).

Experimental Section

Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory. Infrared spectra were recorded as paraffin oil mulls on a P.E. Model 727 spectrophotometer; NMR spectra were obtained in $CDCl_3$ solutions on a P.E. R-600 spectrometer; melting points (Mel-Temp apparatus) were taken in open capillaries and are uncorrected.

3,4-Dimethoxy-6-[(3,4-dimethoxy-6-nitrophenyl)acetyl]-phenylacetic Acid (3). To a paste of keto acid **2** (5 g) in HOAc (15 mL) was added dropwise a cold solution of HNO_3 (5 mL) in HOAc (10 mL) with stirring and cooling in an ice bath. After 20 min, the dark brown solution was poured into cold water (300 mL), and the tan precipitate was collected by suction filtration and washed with water to give the nitro keto acid **3** (4.8 g, 85.7%). The product was recrystallized from dioxane–HOAc as pale yellow crystals: mp 213–214 °C; IR 3355, 1730 (C=O), 1520 and 1330 (NO_2) cm^{-1}; ^1H NMR δ 7.81–6.77 (m, 4 H), 4.64 (s, 2 H), 3.97 (s, $4OCH_3$), 3.78 (s, 2 H). Anal. Calcd for $C_{20}H_{21}NO_9$: C, 57.28; H, 5.05; N, 3.34. Found: C, 57.47; H, 5.13; N, 3.69.

1-(3,4-Dimethoxy-6-nitrobenzyl)-6,7-dimethoxy-3-isochromanone (4). A suspension of nitro keto acid **3** (1.8 g) in EtOH (20 mL) was treated wiith $NaBH_4$ (0.3 g) in small portions. After 3 h additional $NaBH_4$ (0.3 g) was added; after standing for 30 min, the reaction mixture was diluted carefully with water (120 mL), and the solution was acidified with 20% HCl to pH 3. On gentle warming, the nitro lactone (**4**) precipitated as a light yellow solid and was recrystallized from toluene–EtOAc as nearly colorless plates (1.2 g): mp 217–218 °C; IR 1735 (C=O), 1530 (asym NO_2), 1335 (sym NO_2) cm^{-1}; ^1H NMR δ 7.65 (s, 1 H), 6.73 (s, 1 H), 6.63 (s, 1 H), 5.54 (m, 1 H), 3.93 (s, $2OCH_3$), 3.62 (s, 2 H), 3.25 (m, 2 H). Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.55; H, 5.25; N, 3.47. Found: C, 59.21; H, 5.18; N, 3.40.

1-(3,4-Dimethoxy-6-aminobenzyl)-6,7-dimethoxy-3-isochromanone (5). Fe dust (15 g) was added with good mixing to a suspension of nitro lactone **4** (5.2 g) in HOAc (100 mL) at 60 °C over a 1.5-h period. The heating and stirring were continued for 2 h more, and the reaction mixture was added to cold H_2O (700 mL). The solids were collected and extracted with boiling $CHCl_3$ (3 × 30 mL). The $CHCl_3$ extracts were evaporated, and the residue was diluted with hot MeOH, filtered, and cooled to give a tan solid (3.5 g) in several crops. The original aqueous filtrate was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer was evaporated to give an additional 0.8 g of amino lactone **5**. The crude product was recrystallized from EtOH–toluene as colorless crystals: mp 223–224 °C; IR NH_2 doublet at 3500 and 3420, ν_{CO} at 1740 cm^{-1}; ^1H NMR δ 6.61–6.00 (m, 4 H), 5.68 (m, 1 H), 3.84 and 3.80 ($4OCH_3$), 3.52 (s, 2 H), 3.15 (m, 2 H), 2.15 (s, NH_2); mass spectrum, *m/e* (relative intensity) 373 (M^+, 14), 372 (4), 340 (50), 339 (68), 330 (22) 329 (100). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.41; H, 6.19; N, 3.51.

2,3,9,10-Tetramethoxy-6-oxo-5,6,12,12a-tetrahydrodibenzo[*b*,*g*]pyrrocoline (6). (A) In CH_2Cl_2–TFA. Amino lactone **5** (3 g) was dissolved in a solution of CH_2Cl_2 (15 mL)–trifluoroacetic acid (15 mL), and after 18 h, the solution was poured into water (120 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was reextracted with water and evaporated. The residual solids were recrystallized from aqueous MeOH to give a rose-colored product (1.5 g), which was purified by passage through a short column of alumina and recrystallized from MeOH–H_2O as colorless lactam **6** mp 199–200 °C; IR 1655 (C=O) cm^{-1}; mass spectrum *m/e* (relative intensity) 355 (M^+, 100), 340 (93); ^1H NMR δ 7.98 (s, 1 H), 6.85–6.77 (m, 3 H), 5.30 (m, 1 H), 3.95 ($4OCH_3$), 3.69 (s, 2 H), 3.58 (m, 2 H). Anal Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.31; H, 6.04; N, 3.87.

Additional crops of solid (0.3 g) from the methanol solution proved to be starting amino lactone (**5**).

(B) In Toluene–$MgSO_4$. A suspension of **5** (1.0 g) in toluene (50 mL) and anhydrous $MgSO_4$ was allowed to reflux for 24 h. The hot mixture was filtered and was diluted with petroleum ether to 75 mL and cooled. An ivory-colored solid (0.6 g), mp 188–190 °C, was isolated. This product was identical in melting point and IR spectrum with the lactam from part A.

The insoluble solids were extracted with CH_2Cl_2, and starting amino lactone (0.2 g) was recovered on exaporation and recrystallization from EtOH.

***O*-Methylcryptaustoline Iodide (1) and 2,3,9,10-Tetramethoxy-5,6-dihydrodibenzo[*b*,*g*]pyrrocoline (8).** Lactam **6** (1 g) was added to a solution of BH_3–THF complex (35 mL). The solid dissolved only after gentle heating, and the turbid solution was allowed to stand for 20 h. The reaction mixture was hydrolyzed with 10% NaOH and largely evaporated; the residual oil was diluted with water (120 mL) and extracted with CH_2Cl_2 (40 mL). The CH_2Cl_2 solution was divided into two equal parts. One portion was diluted with MeOH (5 mL) and treated with excess MeI. A colorless solid (0.5 g), mp 220–223 °C, separated. The *O*-methylcryptaustoline iodide (**1**) was recrystallized twice from aqueous EtOH as colorless needles: mp 241–243 °C (lit.[11] mp 243–245 °C; lit.[1] mp 242–243 °C); mass spectrum, *m/e* (relative intensity) 341 (M^+ – 142). Anal. Calcd. for $C_{21}H_{26}NO_4 \cdot 0.5\ H_2O$: C, 51.22; H, 5.52; N, 2.85. Found: C, 51.23; H, 5.53; N, 2.88.

The second portion of the CH_2Cl_2 extract was evaporated, and the oily residue was redissolved in MeOH and diluted carefully with water. A light-gray crystalline solid (0.25 g), mp 195–197 °C, separated on standing. The crude solid was chromatographed on silca gel and recrystallized from toluene–hexane solution to give the dihydrodibenzopyrrocoline **8**: mp 204–205 °C (lit.[11] mp 202–204 °C; lit.[1] mp 201–203 °C); mass spectrum, *m/e* (relative intensity) 339 (M^+, 100) 324 (89); ^1H NMR 7.22 (s, 1 H), 7.10 (s, 1 H), 6.80 (s, 1 H), 6.79 (s, 2 H), 3.98 ($4OCH_3$), 4.18 (t, 2 H, J = 6 Hz).

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Registry No. (±)-**1**, 17138-48-6; **2**, 26954-85-8; **3**, 83573-15-3; (±)-**4**, 83573-16-4; (±)-**5**, 83573-17-5; (±)-**6**, 83573-18-6; **8**, 20975-17-1.

Conformation of Long-Chain *erythro*- and *threo*-Tartrates in the Micellar State

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Despite intense current interest in micelles, only two previous reports specifically compare conformations of head-group units inside assemblages with those in the

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