was stirred at room temperature over 30 min and then poured into ice-water. Extraction with ether-dichloromethane (3:1) followed by the usual workup gave an oily residue which was purified by preparative TLC [benzene-ethyl acetate (20:1) with double development] to afford 19.8 mg (38.9%) of **17** and 14.2 mg (27.9%) of **15**. These materials were identical in all respects (TLC, IR, NMR) with their authentic samples.

(b) As above, 20 mg (0.063 mmol) of **24** was reduced with 5 mg of LAH in 1.2 mL of dry tetrahydrofuran and worked up. The crude product was shown to be a 1.5:1 (NMR) mixture of **16a** and **19a** which were, though incompletely separated, identified unambiguously with their authentic samples by NMR and IR data and their TLC behavior.

16-Thia-*D*-homoestrone 3-Methyl Ether (25). A stirred suspension of 50 mg (0.157 mmol) of **20a** and 3 g of silver carbonate-Celite[4] (1 mmol/0.57 g) in 8 mL of dry toluene was heated at gentle reflux under nitrogen for 24 h. The reagent was filtered off, and the toluene was evaporated. The residue was purified through a short column of silica gel (1 g). Elution with benzene gave 14.1 mg of **25** as a crystalline solid, mp 149-152 °C (ether-pentane). The successive fraction which eluted with benzene-ethyl acetate (1:1) yielded 29 mg of recovered **20a**. The total yield of **25** was 67.6% based upon the recovered starting material. Pure **25** was obtained by recrystallization from dichloromethane-ether as a crystalline solid: mp 151-153 °C; NMR δ ($CDCl_3$) 1.20 (s, 3 H, 13-Me), 3.76 (s, 3 H, OMe), 6.6-7.4 (m, 3 H, Ar H); IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, m/e, 316 (M^+). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64; S, 10.13. Found: C, 71.91; H, 7.62; S, 10.16.

Registry No. 1, 64255-74-9; (±)-**2b**, 75878-69-2; (±)-**3b**, 75878-70-5; *meso*-**4a**, 74041-79-5; *meso*-**4b**, 75828-09-0; *meso*-**5a**, 74081-04-2; *meso*-**5b**, 75828-10-3; (±)-**6a**, 75828-11-4; (±)-**6b**, 75828-12-5; (±)-**7a**, 75828-13-6; (±)-**7b**, 75828-14-7; (±)-**8a**, 75828-15-8; (±)-**8b**, 75828-16-9; (±)-**9a**, 75828-17-0; (±)-**9b**, 75828-18-1; (±)-**10a**, 75828-19-2; (±)-**10b**, 75828-20-5; (±)-**11**, 75828-21-6; (±)-**12**, 75828-22-7; (±)-**13a**, 75828-23-8; (±)-**13b**, 75828-24-9; (±)-**14a**, 75828-25-0; (±)-**14b**, 75828-26-1; (±)-**15a**, 75828-27-2; (±)-**15b**, 75828-28-3; (±)-**16a**, 75828-29-4; (±)-**16b**, 75828-30-7; (±)-**17a**, 75828-31-8; (±)-**17b**, 75828-32-9; (±)-**18a**, 75828-33-0; (±)-**18b**, 75828-34-1; (±)-**19a**, 75828-35-2; (±)-**19b**, 75828-36-3; (±)-**20a**, 75828-37-4; (±)-**20b**, 75782-82-0; (±)-**21a**, 75828-38-5; (±)-**21b**, 75782-83-1; (±)-**22a**, 75828-39-6; (±)-**22b**, 75828-40-9; (±)-**23**, 75782-84-2; (±)-**24**, 75828-41-0; (±)-**25**, 75828-42-1; (±)-A, 75790-46-4; (±)-B, 75828-80-7; (±)-C, 75828-81-8; (±)-D, 75828-82-9.

Addition of Dichlorocarbene to Oxyberberine and Berberine

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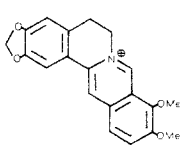
Dichlorocarbene adds to oxyberberine (**2**) to furnish the key adduct **5**. Hydrolysis of **5** in dilute hydrochloric acid yields oxyberberine-13-carboxaldehyde (**7**). Reduction of adduct **5** with zinc in acetic acid produces 13-methyloxyberberine (**11**). Alternatively, reduction of **5** with lithium aluminum hydride in hot THF leads to enlargement of ring C with formation of the vinylic chloride **14**. A complex transformation occurs when **5** is refluxed in aqueous pyridine, the product being keto lactam **15**. Dichlorocarbene in chloroform also adds to berberine (**1**) to form pentachloro derivative **22**. Acid hydrolysis of **22** gives rise to aldehyde **23** which loses hydrogen chloride in the presence of silver oxide to afford dichloro compound **25**. Sodium borohydride reduction of **23** produces alcohol **24**.

As part of a systematic study of the chemistry of berberine (**1**) and its close derivatives, we had occasion to investigate the reaction of oxyberberine (**2**) with dichlorocarbene. It had been previously demonstrated that the adduct **4** was formed in high yield when dichlorocarbene was generated by phase-transfer-catalyzed decomposition of chloroform in the presence of *N*-methylisoquinolone (**3**) and hydroxide ion.[1,2]



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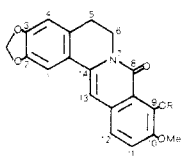
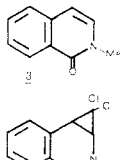


2, R = Me
8, R = H



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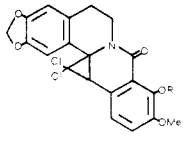
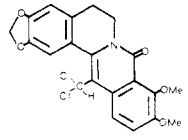
4

When this carbene reaction was extended to the yellow-colored oxyberberine (**2**)[3] using benzyldiethylmethylammonium iodide as catalyst, a colorless crystalline adduct **5** was obtained in 55% yield, ν_{max} ($CHCl_3$) 1648 cm^{-1}. Elemental combustion analysis clearly indicated addition of CCl_2. That the dichloro carbene had added to the C-13,14 double bond of **2** was suggested by the loss of the yellow color in the product, as well as by the fact that the oxyberberine H-13 NMR vinylic singlet at δ 7.18 had moved upfield to δ 3.52 in the adduct **5**.



5, R = Me
9, R = H



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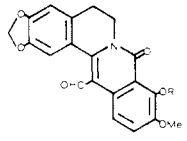


7, R = Me
10, R = H

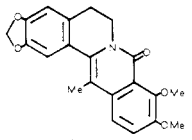
With a reliable supply of adduct **5** on hand, it became logical to envision a series of transformations starting from this adduct which would lead to oxyberberine analogues substituted at C-13. In particular, we became interested in preparing oxyberberine-13-carboxaldehyde (**7**), especially since no 13-carboxaldehyde derivative of berberine or any of its congeners had previously been prepared. Indeed, it was found that when adduct **5** is refluxed in dilute hydrochloric acid in methanol, a 40% yield of the desired yellow aldehyde **7** is obtained, ν_{max} ($CHCl_3$) 1645 cm^{-1} (br), with a characteristic NMR downfield singlet peak at δ 9.77 for the aldehydic proton. This transformation probably proceeds through the intermediacy of the allylic dichloro derivative **6** which can be readily hydrolyzed to the aldehyde **7**.

(1) H.-P. Soetens and U. K. Pandit, *Heterocycles*, 11, 75 (1978).
(2) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(3) W. H. Perkin, Jr., *J. Chem. Soc.*, 722 (1918).

0022-3263/81/1946-0386$01.00/0

When more stringent conditions, such as hot concentrated hydrochloric acid, were used in the opening of the three-membered ring of adduct **5**, two products were obtained. The first proved to be the colorless dichloro derivative **9** of the phenolic compound oxyberberrubine (**8**), ν_{max} ($CHCl_3$) 1635 cm^{-1}, which was isolated in 25% yield. The second and minor product (14%) was the yellow oxyberberrubine-13-carboxaldehyde (**10**), ν_{max} ($CHCl_3$) 1640 and 1660 cm^{-1}. O-Demethylation at C-9 for berberinium salts and their C-8 oxy analogues in the presence of acid is a well-established reaction.[4] It is clear, therefore, that adduct **5** can undergo such a demethylation to supply phenol **9** which can in turn be converted to aldehyde **10**. To further confirm this sequence, it was established that hydrolysis of the phenolic oxy derivative **9** even in dilute hydrochloric acid also supplied aldehyde **10**. Cleavage of the cyclopropane ring is thus best carried out in dilute hydrochloric acid in methanol.

Turning now to the reduction of adduct **5**, it was found that treatment of this compound with zinc in hot acetic acid furnishes pale yellow crystals of 13-methyloxyberberine (**11**), identical with material which had been



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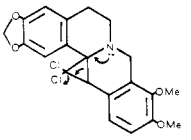

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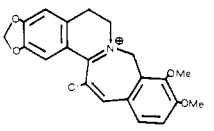

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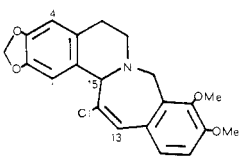
previously prepared in our laboratory through the reaction of 13-methylberberine with aqueous potassium hydroxide.[5] A more interesting transformation occurred upon reduction of **5** with lithium aluminum hydride in hot THF. The product proved to be the colorless C-homoberbine **14** whose NMR spectrum shows characteristic H-13 and H-15 singlets at δ 7.05 and 4.50, respectively. The first step in this transformation must be reduction of the lactam carbonyl to generate amine **12** which can readily eliminate chloride ion to provide iminium cation **13**. This salt is then reduced to provide the C-homoberbine **14** actually isolated.



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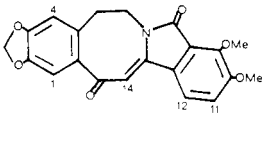

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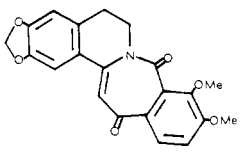

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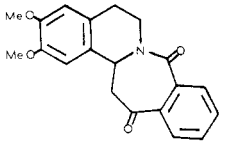

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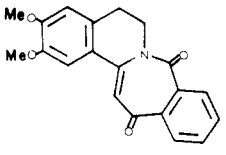

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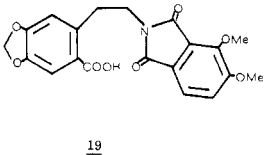

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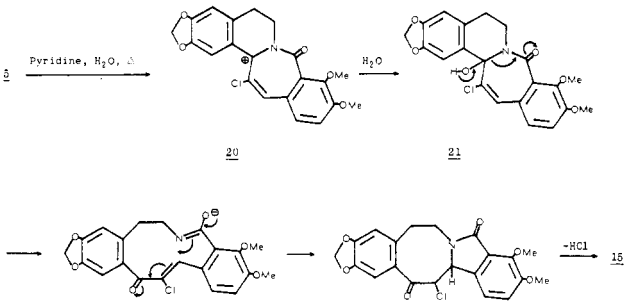
(4) T. R. Govindachari and K. Nagarajan, R. Charubala, and B. R. Pai, *Indian J. Chem.*, 8, 766 (1970).
(5) T.-T. Wu, Ph.D. Thesis, The Pennsylvania State University, 1979, p 137.

Scheme I



In contrast to treatment of adduct **5** with lithium aluminum hydride which results in expansion of ring C of the berbine skeleton, reaction of **5** with hot aqueous pyridine results in expansion of ring B accompanied by contraction of ring C, the product being the keto lactam **15** ν_{max} ($CHCl_3$) 1645 and 1717 cm^{-1}. The NMR spectrum of this yellow compound shows a vinylic singlet absorption at δ 7.17. It was initially difficult to differentiate between structure **15** and the isomeric **16** for the product, especially since **16** would also be expected to show two infrared carbonyl peaks, as well as a vinylic singlet in the NMR spectrum. To settle this structural problem, the known keto lactam **17**[6] was brominated with bromine in acetic acid and then immediately dehydrobrominated in hot dimethyl sulfoxide to supply the light orange keto lactam **18**. Compound **18** is fluorescent under long-wavelength UV light and shows absorption maxima at 212, 265, and 430 nm. Species **15**, on the other hand, shows no fluorescence, and its absorption maxima are at 243 (sh), 270 (sh), 297 (sh), 305, and 375 nm. Final proof of structure for **15** was forthcoming from its oxidation with pyridinium chlorochromate which supplied the known imide **19**[8] whose formation from the alternate structure **16** is not readily explained.

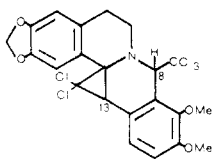
The opening of the cyclopropane ring of adduct **5** in the presence of hot aqueous pyridine can be rationalized in terms of the benzylic cation intermediate **20** which can be hydrated to the unstable chlorohydrin **21**. The latter undergoes fission of the central bond as indicated to supply an eleven-membered ring which is subject to intramolecular condensation and elimination of the elements of hydrogen chloride to provide the keto lactam **15** (Scheme I).[7]

At this stage, our studies were extended to include the reaction of berberine (**1**) with dichlorocarbene, again using benzyldiethylmethylammonium iodide as the phase-transfer catalyst. The transformation proceeded in 50% yield, the colorless adduct being the pentachloro compound **22**. Salient features of the NMR spectrum of **22** are a singlet at δ 3.48, representing H-13, and another singlet at δ 5.00 for H-8.

By analogy with the transformation of the adduct **5** to oxyberberine-13-carboxaldehyde (**7**), it was found that when the pentachloro adduct **22** is refluxed in dilute hydrochloric acid in methanol, yellow crystals of aldehyde **23** are obtained, ν_{max} ($CHCl_3$) 1610 (br) cm^{-1}. Significant peaks in the NMR spectrum are a singlet at δ 5.78 due to H-8 and another singlet downfield at δ 9.48, representing the aldehydic proton.

It is worth noting that the trichloromethyl moiety at C-8 in species **23** is not readily lost as indicated by the finding that sodium borohydride reduction of aldehyde **23** simply leads to the corresponding alcohol **24**, ν_{max} ($CHCl_3$) 3450

(6) M. Shamma and M. J. Hillman, *Tetrahedron*, 27, 1363 (1971).
(7) A somewhat similar rearrangement is discussed in ref 1.



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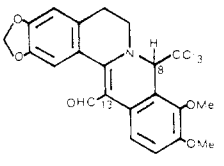
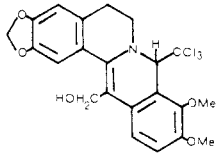


23



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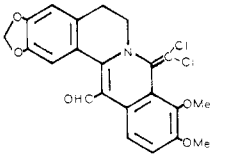

25

cm^{-1}, which is colorless. Alternatively, an attempt to oxidize the aldehyde group of **23** to the carboxylic acid using silver oxide effected instead dehydrochlorination with production of the yellow dichloro derivative **25**.

It is clear from the above that the reaction of dichlorocarbene with oxyberberine and berberine can lead to interesting and unusual derivatives, including in particular the formation of the hitherto unknown C-13 carboxaldehydes.

Experimental Section

General Procedures. Mass spectra were determined at 70 eV. All ultraviolet spectra were obtained in ethanol, and all NMR spectra were taken in deuteriochloroform. TLC was on Merck 254 precoated silica gel plates. Spots were visualized under ultraviolet light or by spraying with chloroplatinate or chromatropic acid sprays. The developing solvent was chloroform–methanol (98:2).

Adduct 5. A solution of 50% sodium hydroxide (6 mL) was added dropwise to a stirred mixture of **2**[3] (1 g, 2.85 mmol) and benzyldiethylmethylammonium iodide (0.1 g, 0.35 mmol) in chloroform (8 mL). Stirring was continued for 2 h at 50 °C. The organic layer was removed, and the aqueous layer extracted with chloroform. The combined organic layer was washed, dried, and evaporated to leave a brown residue which crystallized upon trituration with methanol. Recrystallization from the same solvent yielded colorless needles (0.68 g, 55%): mp 154 °C; R_f 0.60; UV λ_{max} 283 nm (log ϵ 3.77); NMR (60 MHz) δ 2.97 (t, 2 H, J = 6 Hz, H-5), 3.52 (s, 1 H, H-13), 3.88 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.91 (t, 2 H, J = 6 Hz, H-6), 5.93 (s, 2 H, OCH_2O), 6.62 (s, 1 H, H-4), 6.73 (s, 1 H, H-1), 7.04 and 7.23 (AB q, 2 H, J = 8.5 Hz, H-11 and -12).

Anal. Calcd for $C_{21}H_{17}NO_5Cl_2$: C, 55.08; H, 3.94. Found: C, 54.97; H, 3.92.

Oxyberberine-13-carboxaldehyde (7). A solution of **5** (80 mg, 0.18 mmol) in methanol (15 mL) and 10% hydrochloric acid (3 mL) was refluxed for 3 h. After evaporation and extraction with chloroform, the organic layer was washed, dried, and evaporated. The residue was purified by TLC to give a yellow band: R_f 0.47; 38 mg (55%); mp 219 °C (MeOH); UV λ_{max} 218 (sh), 260 (sh), 348 nm (log ϵ 3.50, 3.82, 4.17); NMR (60 MHz) δ 2.88 (t, 2 H, J = 6 Hz, H-5), 3.97 (s, 6 H, 2 OCH_3), 4.20 (t, 2 H, J = 6 Hz, H-6), 6.0 (s, 2 H, OCH_2O), 6.77 (s, 1 H, H-4), 6.83 (s, 1 H, H-1), 7.33 and 8.95 (AB q, 2 H, J = 8 Hz, H-11 and -12), 9.77 (s, 1 H, CHO); high-resolution mass spectrum, calcd for $C_{21}H_{17}NO_6$ 379.1056, found 379.1070.

Phenol 9 and Oxyberberrubine-13-carboxaldehyde (10). A mixture of **5** (80 mg, 0.18 mmol) in concentrated hydrochloric acid (4 mL) was heated at 60 °C for 3 h. After workup, the residue was purified by TLC. A colorless band with R_f 0.64 crystallized from methanol to give **9** (19 mg, 25%) which showed fluorescence under long-wavelength ultraviolet light: mp 168 °C; NMR (60 MHz) δ 2.83–3.03 (m, 2 H, H-5), 3.47 (s, 1 H, H-13), 3.63–3.90 (m, 2 H, H-6), 3.85 (s, 3 H, OCH_3), 5.88 (s, 2 H, OCH_2O), 6.55 (s, 1 H, H-4), 6.68 (s, 1 H, H-1), 6.89 (s, 2 H, H-11 and -12); high-resolution mass spectrum, calcd for $C_{20}H_{15}NO_5Cl_2$ 419.0327, found 419.0348.

A yellow band with R_f 0.61 was also collected and upon crystallization from chloroform–methanol yielded **10** (10 mg, 15%): mp 301–302 °C; NMR (100 MHz) δ 2.97 (t, 2 H, J = 6 Hz, H-5), 3.99 (s, 3 H, OCH_3), 4.22 (m, 2 H, H-6), 6.09 (s, 2 H, OCH_2O), 6.87 (s, 1 H, H-4), 6.88 (s, 1 H, H-1), 7.36 and 8.57 (AB q, 2 H, H-11 and -12), 9.86 (s, 1 H, CHO); high-resolution mass spectrum, calcd for $C_{20}H_{15}NO_6$ 365.0899, found 365.0883.

13-Methyloxyberberine (11). A mixture of **5** (60 mg, 0.14 mmol) and 300 mg of zinc in acetic acid (1.5 mL) was heated at 75 °C for 3 h. The mixture was extracted with chloroform and washed, and the solvent evaporated. Purification by TLC yielded a band, R_f 0.33 (17 mg, 34%), mp 188–189 °C (MeOH–$CHCl_3$), identical with authentic 13-methyloxyberberine[6] and showing blue fluorescence under long-wavelength ultraviolet light.

Conversion of 9 to 10. A solution of **9** (50 mg, 0.12 mmol) in methanol (5 mL) and 10% hydrochloric acid (0.5 mL) was gently refluxed for 2 h. Workup and purification by TLC gave **10** (26 mg, 60%).

Vinyl Chloride 14. A mixture of **5** (125 mg, 0.28 mmol) in THF (20 mL) was refluxed with lithium aluminum hydride (45 mg, 0.39 mmol) for 1 h. Workup and TLC yielded colorless crystals (38 mg, 35%): mp 156–157 °C (hexane); R_f 0.61; UV λ_{max} 250, 282 (log ϵ 3.92, 4.00); NMR (200 MHz) δ 2.67–3.08 (m, 4 H, H-5 and H-6), 3.13 and 4.31 (AB q, 2 H, J = 11.2 Hz, H-8), 3.89 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.50 (s, 1 H, H-15), 5.89 and 5.92 (dd, 2 H, J = 1.5 Hz, OCH_2O), 6.40 (s, 1 H, H-4), 6.61 (s, 1 H, H-1), 6.89 and 6.97 (AB q, 2 H, J = 8.5 Hz, H-11 and -12), 7.05 (s, 1 H, H-13); high-resolution mass spectrum, calcd for $C_{21}H_{20}NO_4Cl$ 385.1080, found 385.1073.

Keto Lactam 15. A solution of **5** (100 mg, 0.23 mmol) in pyridine (4 mL) and water (3 mL) was refluxed for 1 h. Evaporation of the solvent and workup in chloroform gave yellow needles (33 mg, 38%): mp 255 °C ($CHCl_3$–MeOH); R_f 0.55 UV λ_{max} 243 (sh), 270 (sh), 297 (sh), 305, 375 nm (log ϵ 4.13, 3.97, 3.85, 3.86, 4.14); NMR (60 MHz) δ 3.1–3.28 (m, 2 H, H-5), 3.88 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 3.93–4.12 (m, 2 H, H-6), 5.93 (s, 2 H, OCH_2O), 6.22 (s, 1 H, H-4), 6.58 (s, 1 H, H-1), 7.05 and 7.39 (AB q, 2 H, J = 8 Hz, H-11 and -12), 7.17 (s, 1 H, H-14); high-resolution mass spectrum, calcd for $C_{21}H_{17}NO_6$ 379.1038, found 379.1061.

Pentachloro Derivative 22. To a mixture of 1 chloride (1 g, 2.7 mmol) and benzyldiethylmethylammonium iodide (0.1 g, 0.35 mmol) in chloroform (10 mL) was added sodium hydroxide (50% solution, 7 mL) dropwise. The mixture was stirred for 15 h. The organic layer was separated, and the aqueous layer extracted with chloroform. The combined organic layer was washed and dried and the solvent evaporated to leave a brown residue which crystallized from hexane: colorless crystals; mp >200 °C dec (hexane); 0.61 g (42%); R_f 0.70; NMR (60 MHz) δ 2.78–3.08 (m, 2 H, H-5), 3.48 (s, 1 H, H-13), 3.68–3.90 (m, 2 H, H-6), 3.83 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.00 (s, 1 H, H-8), 5.88 (s, 2 H, OCH_2O), 6.47 (s, 1 H, H-4), 6.63 (s, 1 H, H-1), 6.89 and 7.17 (AB q, 2 H, J = 8 Hz, H-11 and -12; mass spectrum (CI), calcd for ($C_{22}H_{18}NO_4Cl_5$ + 1H) 536, found 536.

8-(Trichloromethyl)-7,8-dihydroberberine-13-carboxaldehyde (23). Adduct **22** (1 g, 1.87 mmol) in methanol (50 mL) and hydrochloric acid (10%, 6 mL) was refluxed for 2 h. Evaporation of the solvent and workup followed by TLC gave yellow crystals (0.49 g, 55%): mp 226 °C (MeOH); R_f 0.52; UV λ_{max} 233 (sh), 272, 313, 394 nm (log ϵ 4.20, 3.99, 3.78, 3.63); NMR (60 MHz) δ 2.81–4.13 (m, 4 H, H-5 and H-6), 3.88 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.78 (s, 1 H, H-8), 5.97 (s, 2 H, OCH_2O), 6.72 (s, 1 H, H-4), 7.00 (s, 1 H, H-1), 7.01 and 8.35 (AB q, 2 H, J = 9 Hz, H-11 and -12), 9.48 (s, 1 H, CHO); mass spectrum (CI), calcd for ($C_{22}H_{18}NO_5Cl_3$ + 1H) 482, found 482.

Reduction of 23 to Alcohol 24. A solution of **23** (0.1 g, 0.20 mmol) in methanol (30 mL) was treated with excess sodium borohydride for 3 h. The mixture was diluted with water and extracted with chloroform. The organic layer was dried and the solvent evaporated. Trituration yielded colorless crystals (60 mg, 60%): mp >180 °C dec ($CHCl_3$–MeOH); R_f 0.68; NMR (60 MHz) δ 2.70–2.80 (m, 2 H, H-5), 3.33–3.67 (m, 2 H, H-6), 3.87 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.60–4.73 (m, 2 H, CH_2OH), 5.62 (s, 1 H, H-8), 5.92 (s, 2 H, OCH_2O), 6.62 (s, 1 H, H-4), 6.97 and 7.25 (AB q, 2 H, J = 8.5 Hz, H-11 and -12), 7.33 (s, 1 H, H-1); mass spectrum (CI), calcd for ($C_{22}H_{20}NO_5Cl_3$ + 1 H) 484, found 484

and 448 [(M-35)$^+$]. Alcohol **24** decomposes on standing.

Aldehyde 25. Silver nitrate (100 mg in 1 mL of water) and sodium hydroxide (300 mg in 2 mL of water) were mixed under nitrogen. To this mixture was immediately added **23** (50 mg, 0.1 mmol) in ethanol (6 mL). The mixture was stirred for 5 h with careful heating to 55 °C. Most of the solvent was evaporated at near 55 °C, and the residue extracted with chloroform. Workup, including TLC, gave 28 mg (60%) of yellow crystals: mp >200 °C dec (MeOH); R_f 0.51; UV λ_{max} 243 (sh), 275 (sh), 326, 407 nm (log ϵ 4.19, 3.93, 3.70, 3.10); NMR (200 MHz) δ 2.78–4.19 (m, 4 H, H-5 and -6), 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.06 and 6.08 (dd, 2 H, J = 2 Hz, OCH_2O), 6.79 (s, 1 H, H-4), 7.12 (s, 1 H, H-1), 7.08 and 8.26 (AB q, 2 H, J = 8.8 Hz, H-11 and -12), 9.53 (s, 1 H, CHO); high-resolution mass spectrum, calcd for $C_{22}H_{17}NO_5Cl_2$ 445.0483, found 445.0506.

Conversion of Keto Lactam 17 to 18. Keto lactam **17** (100 mg, 0.29 mmol) in acetic acid (3 mL) was treated with bromine (3–4 drops) in acetic acid (0.5 mL). The solution was stirred for 4 h at near 5 °C, poured into ice water, and extracted with chloroform. The organic layer was dried and the solvent evaporated. Me_2SO (6 mL) was added to the residue, and the solution heated on a steam bath for 10 h. Workup, including TLC, provided a light orange powder, fluorescent under long-wavelength ultraviolet light: 25 mg (25%); mp 276 °C ($CHCl_3$–MeOH), R_f 0.63; UV λ_{max} 212, 265, 430 nm (log ϵ 4.23, 3.85, 3.63); NMR (200 MHz) δ 3.20 (t, 2 H, J = 4.5 Hz, H-5), 3.93 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.35 (br t, 2 H, H-6), 6.72 (s, 1 H, H-4), 7.04 (s, 1 H, H-1), 7.37 (s, 1 H, H-14), 7.72–7.87 (m, 2 H, H-10 and -11), 8.26–8.40 (m, 2 H, H-9 and H-12); high-resolution mass spectrum, calcd for $C_{20}H_{17}NO_4$ 335.1158, found 335.1168.

Oxidation of 15 to Imide 19. To **15** (50 mg, 0.13 mmol) in methylene chloride (10 mL) was added excess pyridinium chlorochromate in portions. The mixture was stirred for 12 h and then extracted with sodium bicarbonate solution. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with chloroform. Workup gave **19** (5 mg, 10%), spectrally identical with an authentic sample.[8]

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Registry No. 1 chloride, 633-65-8; **2**, 549-21-3; **5**, 75767-28-1; **7**, 75767-29-2; **9**, 75767-30-5; **10**, 75767-31-6; **11**, 75767-32-7; **14**, 75767-33-8; **15**, 75767-34-9; **17**, 75767-35-0; **18**, 75767-36-1; **19**, 75767-37-2; **22**, 75767-38-3; **23**, 75767-39-4; **24**, 75767-40-7; **25**, 75767-41-8; dichlorocarbene, 1605-72-7.

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Atropisomerism of Biphenyl Compounds. An Important Role of Ortho-Substituted Methoxy Groups and Fluorine Atoms

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Optically stable atropisomers of 2,2′-difluoro-3,3′-dicarboxy-6,6′-dimethoxybiphenyl (**1**), 2,2′,6,6′-tetramethoxy-3,3′-dicarboxybiphenyl (**3**), and 2,2′,6,6′-tetramethoxy-3,3′-diaminobiphenyl (**4**) were obtained, indicating that ortho-substituted methoxy groups and fluorine atoms are sufficient to allow optical resolution. Furthermore, 2,2′,6-trimethoxy-3-carboxybiphenyl (**6**) was also optically resolvable though less stable than **1** (Tables III and VI).

Some optically active biflavones belonging to the cupressuflavone,[1] agathisflavone,[2] or amentoflavone[3] series have been isolated from natural sources. In these compounds the ortho positions of the pivot linkage are substituted by hydroxy, methoxy, or pyrone-ring oxygen. These facts were inconsistent with the old findings established by Adams and co-workers that fluorine atoms and methoxy groups at the ortho positions of biphenyl compounds do not interfere sufficiently to allow optical resolution. 2,2′-Difluoro-3,3′-dicarboxy-6,6′-dimethoxybiphenyl (**1**),[4] 2,2′,6,6′-tetrafluoro-3,3′-dicarboxy-5,5′-dichlorobiphenyl (**2**),[5] 2,2′,6,6′-tetramethoxy-3,3′-dicarboxybiphenyl (**3**),[6] and 2,2′,6,6′-tetramethoxy-3,3′-diaminobiphenyl (**4**)[6] have been reported to be nonresolvable and these observations are generally accepted.[7] Nevertheless, in the case of optically active amentoflavone (**5**)[3] one of the four ortho positions is unsubstituted (hydrogen). For the settlement of the discrepancy we reinvestigated the optical resolution of these biphenyls (**1**, **3**, and **4**).

Resolution of **3** was first reinvestigated. Contrary to the old report[6] an optically active acid, $[\alpha]^{22}_D$ −18.5° and $[\alpha]^{22}_{400}$ −31.5° ($CHCl_3$), was isolated from a brucine salt. Its dimethyl ester was also optically active, $[\alpha]^{23}_D$ +10.5° and $[\alpha]^{23}_{400}$ +29.5° ($CHCl_3$). Optical purity of the ester was found to be satisfactory from a ^1H NMR study carried out with use of a chiral shift reagent (CSR), tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III).[8] As shown in Table I the active ester showed only one set of signals, while the racemic ester gave two sets of signals. Racemization was not noticeable after the active ester was kept for 90 min at 215 °C in a β-phenylethanol solution. When treated with boiling 0.5 N ethanolic potassium hydroxide the (+)-ester was hydrolyzed to give (−)-acid, identical in rotation with the starting acid.

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