Why Do All Spirobenzylisoquinoline Alkaloids Incorporate a Methylenedioxy Substituent on Ring D?

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Abstract: Treatment of spirobenzylisoquinoline alkaloids **1**, **2**, and **3** with hot methanolic potassium hydroxide provides *o*-methoxyphenols **6**, **7**, and **8**, respectively. Starting with **2** and **3**, and using potassium hydroxide in ethanol, *o*-ethoxyphenols **13** and **14** are produced. A notable feature of the NMR spectra of **13** and **14**, as well as of their acetates **15** and **16**, is that the ethoxy methylene protons appear as a superimposed quartet of quartets due to restricted rotation. The steric compression around any C-9 alkoxy derivative is a factor which encourages formation of the methylenedioxy group from a 9-methoxy-10-hydroxy precursor. Treatment of **6** and **7** with lead tetraacetate produces 13-acetoxyl derivatives **20** and **21**, respectively, with quinodiacetates **22** and **23** as side products. Hydrolysis of **20** and **21** yields alcohols **24** and **25**. Additionally, reaction of **21** with potassium *tert*-butoxide in methanol supplies methyl ether **26**, and reaction of **21** with potassium *tert*-butoxide in ethanol gives rise to ethyl ether **27**, so that the intermediate quinomethide **11** is subject to nucleophilic attack at both C-9 and C-13.

The most salient feature of the 27 known spirobenzylisoquinoline alkaloids is that they all incorporate a methylenedioxy substituent in ring D.[3] It has been established that *o*-methoxyphenols are the biogenetic precursors of aromatic methylenedioxy groups.[4] In many types of natural products, and particularly among the isoquinoline alkaloids, *o*-methoxyphenols, aromatic methylenedioxy groups, and aromatic 1,2-dimethoxy groups are freely encountered.[5] We became interested, therefore, in finding out the exact reasons for the ubiquitous presence of the methylenedioxy group in ring D of the spirobenzylisoquinolines, while at the same time making an effort to cleave selectively this group so as to be able to further functionalize rings C and D of the spirobenzylisoquinoline skeleton.

A premise that was immediately rejected is that there is a special and specific enzyme, present only in spirobenzylisoquinoline bearing plants, that induces formation of the methylenedioxy substituent whenever a spirobenzylisoquinoline species incorporating an *o*-methoxyphenol is encountered. Spirobenzylisoquinolines are found in only two plant genera, *Fumaria* and *Corydalis*, both belonging to the Fumariaceae family, and it was considered unlikely that the same highly specific enzyme would exist in only these two plant genera, and not in others. What is more, the oxygenated substituents at C-2 and C-3 in ring A of the spirobenzylisoquinolines are found as hydroxyl, methoxyl, or methylenedioxy groups, indicating that there is no preference at C-2 and C-3 for the last named substituent.

Rather, it appeared to us as if some intrinsic structural feature were present in ring D of the spirobenzylisoquinolines which encouraged formation of the methylenedioxy group, but which was absent in ring A. In order to determine what this special feature was, it was decided to cleave selectively the ring D methylenedioxy substituent, even when another methylenedioxy was present in ring A.

Since the alkaloid fumariline (**1**) bears a ketone in ring C, it occurred to us that base-catalyzed nucleophilic substitution could be carried out at C-9, i.e., at a site made electron poor due to conjugation with the carbonyl. Indeed, treatment of **1** with hot methanolic potassium hydroxide produced in nearly quantitative yield the *o*-methoxyphenol **6**, in which the integrity of the ring A methylenedioxy group had been maintained. The intermediate in this transformation must be anion **4** which by the electronic shift indicated would lead to hemiacetal **5**. Compound **5** can easily be converted to the product isolated.[6]

In order to prove that the phenolic group in **6** is at C-10 and not at C-9, the UV spectrum was measured in methanol and then in methanol containing hydroxide base. The spectrum of **6** in methanol incorporates an E.T. band at 265 nm. In basic solution, this maximum is shifted to 276 nm. The calculated value for the maximum in neutral solution is:[7] 246 (parent chromophore) + 3 (*o*-alkyl) + 7 (*o*-methoxyl) + 7 (*m*-hydroxyl) = 263 nm. In basic solution, one can calculate in the case of 9-methoxy-10-hydroxy substitution: 246 (parent chromophore) + 3 (*o*-alkyl) + 7 (*o*-methoxyl) + 20 (*m*-oxide anion) = 276 nm. Alternate calculation for the UV maximum in basic solution assuming a phenol at C-9 and a methoxyl at C-10 predicts a value of 267 nm. It follows, therefore, that the methoxyl group is at C-9 and the hydroxyl at C-10 as shown in expression **6**.

As further support for the positions of the methoxyl and hydroxyl groups in **6**, this product was O-methylated with diazomethane to supply dimethoxy derivative **9**. The NMR chemical shifts of the two methoxyl singlets of **9** are δ 3.92 and 4.01. The latter value can be assigned to the C-9 methoxyl which is sterically compressed and whose oxygen is also conjugated with the ring C carbonyl. The chemical shift of the methoxyl singlet in phenol **6** is downfield at δ 4.08, so that this methoxyl too must be located at C-9.

The ring D methylenedioxy cleavage was readily extended to the alkaloid parfumidine (**2**) to provide *o*-methoxyphenol **7**. When potassium hydroxide in ethanol, rather than methanol, was used, the *o*-ethoxyphenol **13** was obtained, again in high yield.

The methylenedioxy cleavage reaction could even be extended to the alkaloid parfumine (**3**) which incorporates a phenolic function at C-2. In this case, and with use of potassium hydroxide in methanol, diphenol **8** was isolated. When ethanol was substituted for methanol, the ethoxydiphenol **14** was produced.

Acetylation of phenols **6**, **8**, **13**, and **14**, with acetic anhydride in pyridine gave single products in each case, namely species **10**, **12**, **15**, and **16**, respectively. A notable characteristic of the NMR spectra of ethoxyphenols **13** and **14**, as well as of their acetates **15** and **16**, is that the ethoxyl methylene protons show a complex splitting pattern, in reality a superimposed quartet of quartets centered near δ 4.25, due to restricted rotation. Ring D in all spirobenzylisoquinolines is uniformly tetrasubstituted in a vicinal sequence. Additionally, the adjoining five-membered ring usually possesses a carbonyl or alcohol function at C-8, as well as the bulky tetrahydroisoquinoline moiety at C-14. The high degree of sub-

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(3) For a listing of spirobenzylisoquinoline alkaloids and their spectral data, see: R. M. Preisner and M. Shamma, *J. Nat. Prod.*, 43, 305 (1980).
(4) D. H. R. Barton, *Proc. Chem. Soc. London*, 293 (1963); D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *ibid.*, 267 (1963).
(5) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p 380; and M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research *1972–1977*", Plenum Press, New York, 1978, p 325.
(6) S. Kobayashi, Y. Imakura, and R. Horikawa, *Chem. Pharm. Bull.*, **28**, 1287 (1980). See also W. D. Crow and J. R. Price, *Aust. J. Sci. Res., Ser. A*, **2**, 282 (1949).
(7) A. I. Scott, "Interpretation of the UV Spectra of Natural Products", Pergamon Press, Oxford, 1964, Table 3.4c.

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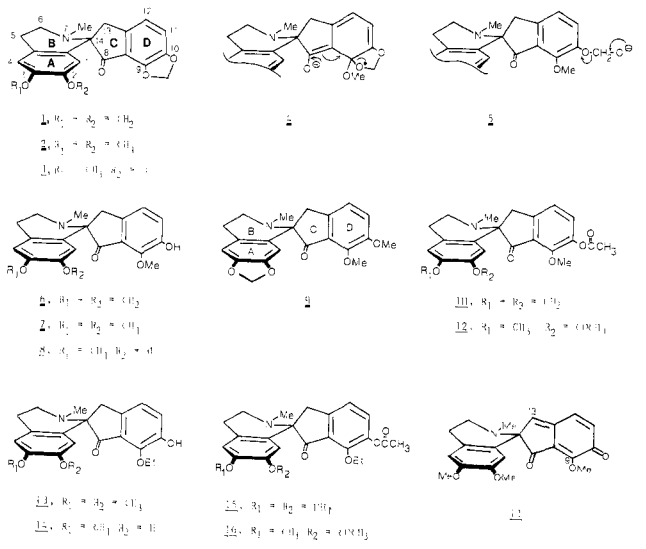
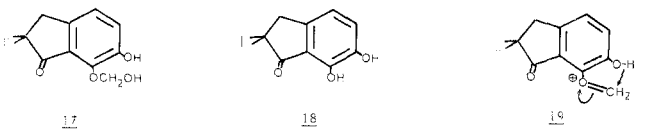
stitution thus results in steric compression around any C-9 alkoxy substituent. Such compression is brought to the fore in the ethoxyl series, resulting in the observable complex NMR pattern just mentioned. It is this special, highly sterically crowded, feature of spirobenzylisoquinolines that gives the clue as to the facile formation of the methylenedioxy group in ring D. The precursors for alkaloids **1–3** in the plant are most probably *o*-methoxyphenols **6–8**, respectively. The relief in steric compression is so substantial in going from the *o*-methoxyphenol to the corresponding aromatic methylenedioxy compound that such a transformation is readily accomplished with the added assistance of the proper enzyme.



Steric compression is obviously absent in ring A, so that this ring's substituents are found indiscriminately as hydroxyl, methoxyl, or methylenedioxy functions.

A probable route for the actual transformation in nature of *o*-methoxyphenols **6–8** into alkaloids **1–3** involves enzymatic formation of hemiacetal **17**[8] which can, a priori, either lose formaldehyde to form diphenol **18**, or undergo dehydration to oxonium ion **19**. The latter species can then cyclize to furnish methylenedioxy-bearing alkaloids **1–3**. It should be mentioned that *o*-methoxyphenols **6–8** are more likely biogenetic precursors than the *o*-methoxyphenols in which the phenolic group would be located at C-9 and the methoxyl at C-10. In such an alternate arrangement, the methoxyl group would be pointing away from the phenolic function and toward H-11, and would therefore be under less steric constraint to transform itself into a methylenedioxy substituent.

A corollary of the above discussion is that enzymatic O-demethylation appears to be closely related to enzymatic methylenedioxy formation since both processes involve the intermediacy of a hemiacetal such as in **17**, derived from oxidation of a methoxyl group.



With the fission of the methylenedioxy group of ring D, the stage was set for the further functionalization of the spirobenzylisoquinolines. Treatment of *o*-methoxyphenols **6** and **7** with 1 equiv of lead tetraacetate in acetic acid at room temperature produced in ~70% yields the 13-acetoxyl spiro derivatives **20** and **21**, respectively. Interestingly, the side products (8–10%) were quinodiacetates **22** and **23**. Some features of the NMR spectra of quinodiacetates **22** and **23** deserve special comment. The C-9 methoxyl singlet is found in both instances upfield at δ 3.54. Also, the H-11 and H-12 coupling constant is 10 Hz rather than the usual 8 Hz expected for aromatic ortho-coupled protons.

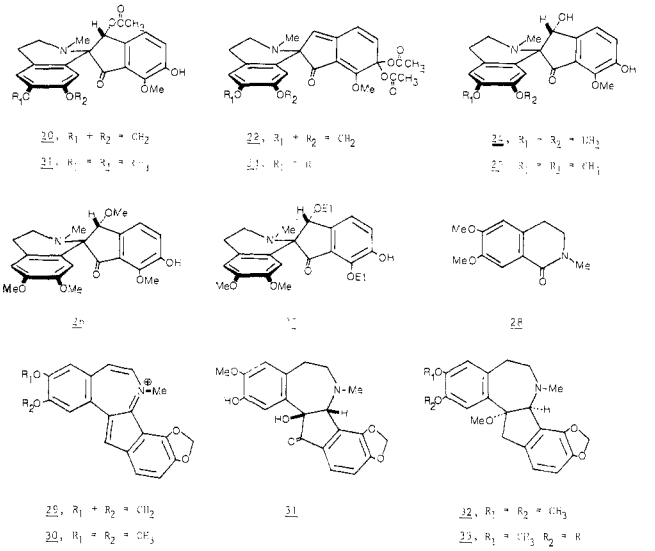
Mild acid hydrolysis of acetates **20** and **21** generated the corresponding alcohols **24** and **25**, respectively. This further functionalization of ring C of spirobenzylisoquinolines is particularly appropriate since all of the spirobenzylisoquinoline alkaloids derived from *Corydalis* species are known to be dioxygenated in ring C, while those originating from *Fumaria* species bear only one oxygen in that ring.[3]

It will be noted that the 13-acetoxyl group in species **20** and **21** has been placed in a syn position, i.e., on the same side as the nitrogen atom. This conclusion is based on the fact that the stereochemistry of the lead tetraacetate oxidation reaction is dependent upon steric approach control, with acetic acid adding from the less hindered nitrogen side of the molecule.[5] Characteristically, H-13 in acetoxyl derivatives **20** and **21** are found at δ 6.07 and 6.04, respectively, a clear indication of the syn relationship of these hydrogens to the nitrogen atoms. Likewise, H-13 in hydroxyl derivatives **24** and **25** fall at δ 4.93 and 5.08, respectively.[3]

It was also established that the 13-acetoxyl group in spirobenzylisoquinoline **21** can be readily substituted with another function. For example, treatment of **21** with a mixture of potassium *tert*-butoxide in methanol supplied methyl ether **26** which is formed via *p*-quinomethide **11** so that the methoxyl group lies syn to the nitrogen atom.

A more telling transformation is that taking place upon reaction of **21** with a mixture of potassium *tert*-butoxide in ethanol, in which ethyl ether **27** is produced. The fact that two ethoxyl groups are present in species **27** is a clear indication that the intermediate *p*-quinomethide **11** is subject to nucleophilic attack at both C-9 and C-13.

In each of the above two transformations (**21** → **26** and **21** → **27**), a side product was the isoquinoline **28**, *N*-methylcorydaldine, which is known as a natural product,[9] and which could very well be formed in nature as a final catabolic product from the oxidation of spirobenzylisoquinoline and other isoquinoline alkaloids. In the potassium *tert*-butoxide in methanol reaction, this product was obtained in lesser amounts than when ethanol was the solvent. However, in potassium *tert*-butoxide in 2-propanol or in *tert*-butyl alcohol, *N*-methylcorydaldine was the only product obtained, even when the reaction was run in an essentially nitrogen atmosphere.



It should be noted in conclusion that members of the newly recognized class of indenobenzazepine alkaloids, which presently include lahorine (**29**), lahoramine (**30**), fumarofine (**31**), fu-

(8) For a discussion of the enzymatic formation of hemiacetals from aromatic methoxyl groups, see F.-H. Bernhardt, H. Staundiger, and V. Ullrich, *Hoppe-Seyler's Z. Physiol. Chem.*, **351**, 467 (1970); and F.-H. Bernhardt and E. Heymann, *IRCS Med. Sci.: Libr. Compend.*, 3, 463 (1975).

(9) M. Shamma and Sr. M. A. Podczasy, *Tetrahedron*, **27**, 727 (1971). *N*-Methylcorydaldine has also been obtained as colorless prisms, mp 125–126 °C (petroleum ether), see E. Späth and H. Epstein, *Chem. Ber.*, **59**, 279 (1926).

maritrine (**32**), and fumaritridine (**33**), also incorporate a methylenedioxy group in ring D.[10-12] Since spirobenzylisoquinolines are almost certainly the biogenetic precursors of the indenobenzazepines, it is obvious that the methylenedioxy group of the former alkaloid class is carried intact into the latter.

Experimental Section

General Procedures. Melting points are uncorrected. NMR data were collected on a Bruker 200 MHz Supercon (FT) spectrometer in $CDCl_3$ solution, using Me_4Si as internal standard. Mass spectra were taken with an AEI MS-902 instrument. The circular dichroism measurements were done on a JASCO-20 spectropolarimeter. The ultraviolet spectra were recorded with a Hewlett-Packard 8450A UV/VIS spectrophotometer; wavelengths are in nanometers. All UV and CD curves were taken in methanol. The TLC R_f values given were obtained on silica gel HLF-Uniplates (Analtech) in benzene–methanol 100:15 (v/v). Preparative TLC was on silica gel F-254 Merck plates, using the above system. Infrared spectra were recorded in chloroform solution. Elemental analyses are by high-resolution mass spectroscopy.

General Reaction Procedure for the Cleavage of the 9,10-(Methylenedioxy) Ring. The alkaloid (**1**, **2**, or **3**) was dissolved in absolute methanol or ethanol and 5 equiv of solid potassium hydroxide was added. The mixture was refluxed for 5 h, allowed to sit at room temperature for 1 h, and then acidified with methanolic hydrogen chloride. The solvent was removed in vacuo. The residue was dissolved in a minimum amount of water, basified with ammonium hydroxide, and then extracted with chloroform. Removal of the solvent gave a pale yellow viscous oil which was purified by preparative TLC to give the desired product in 75–82% yields.

2,3-(Methylenedioxy)-8-keto-9-methoxy-10-hydroxyspirobenzylisoquinoline (6): $C_{20}H_{19}O_5N$; mp 194–195 °C (MeOH); λ_{max} 221 (sh), 265, 294 (sh), and 342 nm (log ϵ 4.38, 4.07, 3.70, and 3.47); NMR δ 2.35 (s, 3 H, N–CH_3), 4.08 (s, 3 H, 9-OCH_3), 5.86 and 5.83 (q, J_{gem} = 1.3 Hz, 2 H, OCH_2O), 6.17 (s, 1 H, H-1), 6.58 (s, 1 H, H-4), 7.08 (d, J = 8.1 Hz, 1 H, H-12), 7.30 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 353 (M^+, 48), 326 (37), 324 (100), 310 (10), 294 (6), 188 (7), 175 (12); CD $\Delta\epsilon_{nm}$ $+2.50_{236}$, -4.06_{268}, -4.42_{302}, $+0.36_{350}$; R_f 0.49.

2,3,9-Trimethoxy-8-keto-10-hydroxyspirobenzylisoquinoline (7): $C_{21}H_{23}O_5N$; mp 222–223 °C (MeOH); λ_{max} 224, 263, 290 (sh), and 340 nm (log ϵ 4.42, 4.07, 3.68, and 3.45); NMR δ 2.36 (s, 3 H, N–CH_3), 3.55 (s, 3 H, 2-OCH_3), 3.85 (s, 3 H, 3-OCH_3), 4.08 (s, 3 H, 9-OCH_3), 6.16 (s, 1 H, H-1), 6.61 (s, 1 H, H-4), 7.11 (d, J = 8.1 Hz, 1 H, H-12), 7.31 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 369 (M^+, 44), 341 (32), 340 (47), 326 (36), 310 (100), 296 (17), 281 (8), 191 (17); CD $\Delta\epsilon_{nm}$ $+2.79_{236}$, -6.72_{263}, -5.01_{295}, $+0.57_{340}$; R_f 0.41.

2,10-Dihydroxy-3,9-dimethoxy-8-ketospirobenzylisoquinoline (8): $C_{20}H_{21}O_5N$; mp 244–246 °C (MeOH); λ_{max} 220 (sh), 262, 292 (sh), and 338 nm (log ϵ 4.31, 3.97, 3.56, and 3.44); NMR δ 2.34 (s, 3 H, N–CH_3), 3.85 (s, 3 H, 3-OCH_3), 4.06 (s, 3 H, 9-OCH_3), 6.29 (s, 1 H, H-1), 6.59 (s, 1 H, H-4), 7.06 (d, J = 8.0 Hz, 1 H, H-12), 7.28 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 355 (M^+, 62), 327 (42), 325 (100), 310 (36), 295 (11), 252 (3); CD $\Delta\epsilon_{nm}$ -5.15_{271}, -5.08_{298}, $+0.34_{340}$; R_f 0.30.

2,3-(Methylenedioxy)-8-keto-9,10-dimethoxyspirobenzylisoquinoline (9). An ethereal solution of **6** (11 mg, 0.03 mmol) was treated with excess diazomethane in ether for 30 h. After removing the solvent, the residue was purified by TLC to supply **9** (1.2 mg, 11%) and unreacted **6** (8.5 mg, 77%).

9: amorphous; $C_{21}H_{21}O_5N$; λ_{max} 215 (sh), 256, 288, and 330 nm (log ϵ 4.26, 3.93, 3.64, and 3.40); NMR δ 2.36 (s, 3 H, N–CH_3), 3.92 (s, 3 H, 10-OCH_3), 4.01 (s, 3 H, 9-OCH_3), 5.83 and 5.86 (q, J_{gem} = 1.3 Hz, 2 H, OCH_2O), 6.17 (s, 1 H, H-1), 6.58 (s, 1 H, H-4), 7.13 (d, J = 8.1 Hz, 1 H, H-12), 7.23 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 367 (M^+, 28), 339 (30), 338 (100), 324 (37), 310 (10), 308 (18), 292 (6); R_f 0.60.

2,3-Dimethoxy-8-keto-9-ethoxy-10-hydroxyspirobenzylisoquinoline (13): $C_{22}H_{25}O_5N$, amorphous; λ_{max} 220 (sh), 264, 292 (sh), and 342 nm (log ϵ 4.41, 4.17, 3.62, and 3.55); NMR δ 1.39 (t, J = 7.0 Hz, 3 H, CH_3), 2.35 (s, 3 H, N–CH_3), 3.54 (s, 3 H, 2-OCH_3), 3.84 (s, 3 H, 3-OCH_3), 4.29 and 4.30 (qq, J_1 = 7.0 Hz, J_2 = 14.0 Hz, 2 H, CH_2), 6.15 (s, 1 H, H-1), 6.60 (s, 1 H, H-4), 7.09 (d, J = 8.0 Hz, 1 H, H-12), 7.30 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 383 (M^+, 72), 368 (18), 354 (62), 352 (24), 340 (100), 327 (64), 326 (59), 310 (21), 295 (22), 204 (19), 191 (30); CD $\Delta\epsilon_{nm}$ -5.26_{268}, -5.18_{269}, $+0.21_{340}$; R_f 0.43.

2,10-Dihydroxy-3-methoxy-8-keto-9-ethoxyspirobenzylisoquinoline (14): $C_{21}H_{23}O_5N$; amorphous, λ_{max} 220 (sh), 262, 292 (sh), 340 nm (log ϵ 4.28, 392, 3.49, and 3.35); NMR δ 1.39 (t, J = 7.0 Hz, 3 H, CH_3), 2.33 (s, 3 H, N–CH_3), 3.83 (s, 3 H, 3-OCH_3), 4.27 and 4.29 (qq, J_1 = 7.0 Hz, J_2 = 13.8 Hz, 2 H, CH_2), 6.28 (s, 1 H, H-1), 6.58 (s, 1 H, H-4), 7.06 (d, J = 8.1 Hz, 1 H, H-12), 7.28 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 369 (M^+, 94), 354 (14), 341 (44), 340 (100), 325 (60), 324 (48), 313 (60), 295 (13), 291 (11); CD $\Delta\epsilon_{nm}$ -5.12_{268}, -5.07_{295}, $+0.27_{338}$; R_f 0.38.

General Acetylation Procedure. The compound (**6**, **8**, **13**, or **14**) was dissolved in the minimum amount of dry pyridine and excess acetic anhydride added. After the solution had stood overnight, the solvent was removed under vacuo and the residue was purified by preparative TLC to give the acetylated product as an oil in 70–77% yields.

2,3-(Methylenedioxy)-8-keto-9-methoxy-10-acetoxyspirobenzylisoquinoline (10): $C_{22}H_{21}O_6N$; λ_{max} 220 (sh), 260, 292, and 336 nm (log ϵ 4.32, 3.99, 3.68, and 3.37); NMR δ 2.33 (s, 3 H, $COCH_3$), 2.36 (s, 3 H, N–CH_3), 4.08 (s, 3 H, 9-OCH_3), 5.83 and 5.86 (q, J_{gem} = 1.3 Hz, 2 H, OCH_2O), 6.17 (s, 1 H, H-1), 6.58 (s, 1 H, H-4), 7.08 (d, J = 8.0 Hz, 1 H, H-12), 7.30 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 395 (M^+, 23), 366 (58), 325 (34), 324 (100), 310 (13), 295 (12), 252 (6); R_f 0.65.

2,10-Diacetoxy-3,9-dimethoxy-8-ketospirobenzylisoquinoline (12): $C_{24}H_{25}O_7N$; λ_{max} 217, 257, 288 (sh), and 324 nm (log ϵ 4.31, 3.94, 3.57, and 3.35); NMR δ 2.20 (s, 3 H, $COCH_3$), 2.22 (s, 3 H, $COCH_3$), 2.36 (s, 3 H, N–CH_3), 3.80 (s, 3 H, 3-OCH_3), 4.06 (s, 3 H, 9-OCH_3), 6.36 (s, 1 H, H-1), 6.71 (s, 1 H, H-4), 7.11 (d, J = 8.0 Hz, 1 H, H-12), 7.30 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 439 (M^+, 30.0), 411 (13), 398 (24), 397 (91), 382 (13), 369 (55), 354 (39), 338 (33), 326 (100), 310 (48), 295 (12), 278 (12); R_f 0.51.

2,3-Dimethoxy-8-keto-9-ethoxy-10-acetoxyspirobenzylisoquinoline (15): $C_{24}H_{27}O_6N$; λ_{max} 218, 256, 290 (sh), and 315 nm (log ϵ 4.53, 4.11, 3.62, and 3.46); NMR δ 1.34 (t, J = 7.0 Hz, 3 H, CH_3), 2.34 (s, 3 H, N–CH_3), 2.35 (s, 3 H, $COCH_3$), 3.57 (s, 3 H, 2-OCH_3), 3.84 (s, 3 H, 3-OCH_3), 4.20 and 4.22 (qq, J_1 = 7.0 Hz, J_2 = 13.5 Hz, 2 H, CH_2), 6.13 (s, 1 H, H-1), 6.60 (s, 1 H, H-4), 7.17 (d, J = 8.0 Hz, 1H, H-12), 7.35 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 425 (M^+, 53), 410 (17), 397 (34), 396 (45), 382 (100), 366 (62), 354 (47), 340 (57), 327 (79), 326 (31), 311 (21), 294 (11), 204 (17), 191 (20); R_f 0.56.

2,10-Diacetoxy-3-methoxy-8-keto-9-ethoxyspirobenzylisoquinoline (16): $C_{25}H_{27}O_7N$; λ_{max} 220 (sh), 261, 290 (sh), and 331 nm (log ϵ 4.30, 3.95, 3.54, and 3.32); NMR δ 1.43 (t, J = 7.0 Hz, 3 H, CH_3), 2.20 (s, 3 H, $COCH_3$), 2.22 (s, 3 H, $COCH_3$), 2.33 (s, 3 H, N–CH_3), 3.80 (s, 3 H, 3-OCH_3), 4.23 and 4.25 (qq, J_1 = 7.0 Hz, J_2 = 14.0 Hz, 2 H, CH_2), 6.35 (s, 1 H, H-1), 6.70 (s, 1 H, H-4), 7.07 (d, J = 8.1 Hz, 1 H, H-12), 7.31 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 453 (M^+, 27), 412 (24), 411 (100), 395 (15), 3.92 (61), 368 (65), 355 (86), 340 (77), 324 (37), 312 (21), 295 (18); R_f 0.52.

2,3-(Methylenedioxy)-8-keto-9-methoxy-10-hydroxy-*syn*-13-acetoxyspirobenzylisoquinoline (20). Compound **6** (46 mg, 0.13 mmol) was dissolved in glacial acetic acid (15 mL) and lead tetraacetate (63 mg, 0.14 mmol) added. The mixture was allowed to stand overnight at room temperature. It was then diluted with chloroform and the acetic acid neutralized with saturated aqueous sodium carbonate. After extraction, the organic layer was dried, evaporated in vacuo, and the remaining material purified by TLC to yield **20** (39 mg, 72%) and **22** (5.3 mg, 9%).

20: $C_{22}H_{21}O_7N$; mp 158–159 °C; λ_{max} 221, 261, 292, and 336 nm (log ϵ 4.40, 4.05, 3.81, and 3.60); ν_{max} 1740 and 1700 cm^{-1}; NMR δ 2.13 (s, 3 H, $COCH_3$), 2.32 (s, 3 H, N–CH_3), 4.12 (s, 3 H, 9-OCH_3), 5.83 and 5.86 (q, J_{gem} = 1.1 Hz, 2 H, OCH_2O), 6.07 (s, 1 H, H-13), 6.10 (s, 1 H, H-1), 6.58 (s, 1 H, H-4), 7.26 (d, J = 8.2 Hz, 1 H, H-12), 7.38 (d, J = 8.2 Hz, 1 H, H-11); mass spectrum m/e 411 (M^+, 14.4), 368 (12), 352 (11), 204 (6), 190 (8), 69 (53), 45 (100); CD $\Delta\epsilon_{nm}$ -6.64_{222}, $+4.15_{238}$, -3.65_{266}, -3.57_{304}, -4.32_{328}, $+1.41_{390}$; R_f 0.58.

22: $C_{24}H_{23}O_8N$; amorphous λ_{max} 235 (sh), 294, and 369 nm (log ϵ 4.18, 3.71, and 3.34); ν_{max} 1740 (sh), 1730, and 1695 cm^{-1}; NMR δ 2.12 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.42 (s, 3 H, N–CH_3), 3.54 (s, 3 H, 9-OCH_3), 5.68 (s, 1 H, H-13), 5.87 (s, 2 H, OCH_2O), 6.15 (s, 1 H, H-1), 6.54 (s, 1 H, H-4), 6.54 (d, J = 10.0 Hz, 1 H, H-12), 7.19 (d, J = 10.0 Hz, 1 H, H-11); mass spectrum m/e 453 (M^+, 2), 411 (8), 368 (13), 351 (19), 337 (47), 308 (27), 280 (17), 149 (100); R_f 0.69.

2,3,9-Trimethoxy-8-keto-10-hydroxy-*syn*-13-acetoxyspirobenzylisoquinoline (21). Starting with **7** (67 mg, 0.18 mmol) and using lead tetraacetate (88.5 mg, 0.20 mmol) in glacial acetic acid (15 mL) a similar sequence gave **21** (54.3 mg, 70%) and **23** (6.9 mg, 8%).

21: $C_{23}H_{25}O_7N$; mp 169–170 °C (MeOH); λ_{max} 223, 262, 293 (sh), and 333 nm (log ϵ 4.49, 4.13, 3.80, and 3.57); ν_{max} 1740 and 1700 cm^{-1}; NMR δ 2.15 (s, 3 H, $COCH_3$), 2.47 (s, 3 H, N–CH_3), 3.57 (s, 3 H, 2-OCH_3), 3.85 (s, 3 H, 3-OCH_3), 4.12 (s, 3 H, 9-OCH_3), 6.04 (s, 1 H,

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H-13), 6.25 (s, 1 H, H-1), 6.63 (s, 1 H, H-4), 7.29 (d, J = 8.1 Hz, 1 H, H-12), 7.40 (d, J = 8.1 Hz, 1 H, H-11); mass spectrum m/e 427 (M^+, 24), 384 (28), 369 (12), 368 (44), 367 (56), 354 (57), 352 (100), 340 (28), 339 (30), 338 (43), 324 (37), 294 (22); CD $\Delta\epsilon_{nm}$ -6.53_{217}, $+3.86_{239}$, -2.75_{270}, -2.36_{292}, -3.38_{328}, $+1.49_{392}$; R_f 0.49.

23: $C_{25}H_{27}O_8N$; amorphous; λ_{max} 235 (sh), 292, and 372 nm (log ϵ 4.24, 3.69, and 3.27); ν_{max} 1740, 1730, and 1695 cm^{-1}; NMR δ 2.09 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$), 2.44 (s, 3 H, N-CH_3), 3.54 (s, 3 H, 9-OCH_3), 3.73 (s, 3 H, 2-OCH_3), 3.84 (s, 3 H, 3-OCH_3), 5.73 (s, 1 H, H-13), 6.12 (s, 1 H, H-1), 6.57 (s, 1 H, H-4), 6.55 (d, J = 10.0 Hz, 1 H, H-12), 7.22 (d, J = 10.0 Hz, 1 H, H-11); mass spectrum m/e 469 (M^+, 1.4), 442 (2), 425 (2), 383 (3), 367 (4), 352 (6), 308 (1), 278 (3), 221 (5), 150 (9); R_f 0.67.

2,3-(Methylenedioxy)-8-keto-9-methoxy-10-hydroxy-*syn*-13-hydroxyspirobenzylisoquinoline (24). Compound **20** (12 mg, 0.03 mmol) was dissolved in 5% aqueous hydrogen chloride (1 mL) and kept at room temperature overnight. Workup including TLC gave **24** (7.8 mg, 72%).

24: $C_{20}H_{19}O_6N$; amorphous; λ_{max} 227, 265, 293, and 335 nm (log ϵ 4.52, 3.98, 3.67, and 3.40); NMR δ 2.25 (s, 3 H, N-CH_3), 4.12 (s, 3 H, 9-OCH_3), 4.93 (s, 1 H, H-13), 5.88 and 5.89 (q, J_{gem} = 1.2 Hz, 2 H, OCH_2O), 6.13 (s, 1 H, H-1), 6.59 (s, 1 H, H-4), 7.38 (s, 2 H, H-11 and H-12); mass spectrum m/e 369 (M^+, 30), 354 (35), 336 (10), 324 (39), 308 (22), 204 (25), 190 (100), 149 (16); CD $\Delta\epsilon_{nm}$ -5.13_{267}, -5.26_{331}, $+2.10_{380}$; R_f 0.52.

2,3,9-Trimethoxy-8-keto-10-hydroxy-*syn*-13-hydroxyspirobenzylisoquinoline (25). Compound **21** (8.5 mg, 0.03 mmol) was dissolved in 5% aqueous hydrogen chloride (1 mL) and kept at room temperature overnight. Workup including TLC supplied **25** (5.9 mg, 77%).

25: $C_{21}H_{23}O_6N$; amorphous; λ_{max} 225 (sh), 265, 293, and 336 nm (log ϵ 4.49, 4.02, 3.51, and 3.42); ν_{max} 1700 and 3500 cm^{-1}; NMR δ 2.41 (s, 3 H, N-CH_3), 3.60 (s, 3 H, 2-OCH_3), 3.85 (s, 3 H, 3-OCH_3), 4.09 (s, 3 H, 9-OCH_3), 5.08 (s, 1 H, H-13), 6.07 (s, 1 H, H-1), 6.62 (s, 1 H, H-4), 7.41 (s, 2 H, H-11 + H-12); mass spectrum m/e 385 (M^+, 54), 370 (58), 354 (10), 342 (16), 340 (38), 324 (18), 310 (11), 220 (35), 206 (100), 190 (24); CD $\Delta\epsilon_{nm}$ $+1.79_{237}$, -5.22_{270}, -6.60_{332}, $+1.79_{385}$; R_f 0.40.

2,3,9-Trimethoxy-8-keto-10-hydroxy-*syn*-13-methoxyspirobenzylisoquinoline (26). Compound **21** (13 mg, 0.03 mmol) dissolved in dry methanol (6 mL) was refluxed in the presence of potassium *tert*-butoxide (10 mg, 0.09 mmol) for 8 h. The reaction mixture was cooled and neutralized with methanolic hydrogen chloride. The solvent was removed in vacuo and the residue extracted with chloroform. The organic layer was dried, evaporated, and purified by TLC to supply **26** (5.5 mg, 45%) and **28** (1.2 mg, 18%).

26: $C_{22}H_{25}O_6N$; amorphous; λ_{max} 225 (sh), 260, 291, and 334 nm (log ϵ 4.47, 4.00, 3.53, and 3.41); NMR δ 2.31 (s, 3 H, N-CH_3), 3.51 (s, 3 H, 13-OCH_3), 3.64 (s, 3 H, 2-OCH_3), 3.86 (s, 3 H, 3-OCH_3), 4.92 (s, 1 H, H-13), 6.09 (s, 1 H, H-1), 6.63 (s, 1 H, H-4), 7.32 (d, J = 8.0 Hz, 1 H, H-12), 7.35 (d, J = 8.0 Hz, 1 H, H-11); mass spectrum m/e 399 (M^+, 49), 384 (38), 367 (20), 353 (27), 352 (37), 340 (100), 325 (23), 310 (21), 294 (14), 265 (10), 220 (10), 206 (28); CD $\Delta\epsilon_{nm}$ $+2.59_{230}$, -3.11_{267}, -5.49_{330}, $+1.97_{395}$; R_f 0.52.

2,3-Dimethoxy-8-keto-9-ethoxy-10-hydroxy-*syn*-13-ethoxyspirobenzylisoquinoline (27). Compound **21** (17 mg, 0.4 mmol) dissolved in dry ethanol (8 mL) was refluxed in the presence of potassium *tert*-butoxide (13.5 mg, 0.12 mmol) for 8 h. After workup, including purification by TLC, **27** (3.6 mg, 21.2%) and **28** (3.2 mg, 36%) were obtained.

27: $C_{24}H_{29}O_6N$; amorphous; λ_{max} 221, 256, 295 (sh), and 330 nm (log ϵ 4.35, 3.96, and 3.41); NMR δ 1.21 (t, J = 7.0 Hz, 3 H, CH_3), 1.40 (t, J = 7.0 Hz, 3 H, CH_3), 2.35 (s, 3 H, N-CH_3), 3.62 (s, 3 H, 2-OCH_3), 3.86 (s, 3 H, 3-OCH_3), 4.28-4.39 (m, 4 H, 2 × CH_2), 5.00 (s, 1 H, H-13), 6.06 (s, 1 H, H-1), 6.63 (s, 1 H, H-4), 7.32 (d, J = 8.2 Hz, 1 H, H-12), 7.37 (d, J = 8.2 Hz, 1 H, H-11); mass spectrum m/e 427 (M^+, 6.4), 397 (9.4), 354 (17), 322 (3), 207 (29), 169 (60); CD $\Delta\epsilon_{nm}$ $+1.50_{228}$, -3.64_{269}, -6.26_{330}, $+1.01_{395}$; R_f 0.50.

28: $C_{12}H_{15}O_3N$; amorphous; NMR δ 3.14 (s, 3 H, N-CH_3), 3.92 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.64 (s, 1 H, H-5), 7.61 (s, 1 H, H-8); mass spectrum m/e 221 (M^+, 65), 219 (17), 178 (81), 150 (100), 135 (18), 107 (11); R_f 0.51.

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Synthesis, Conformation, and Complexation Behavior of 2,9,18,25-Tetraoxa-33,34,35,36-tetrakis(acyloxymethyl)[8.8]-(1,4)naphthalenophanes[1]

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Abstract: Title compounds with acetate, propionate, phenylacetate, *p*-bromophenylacetate, and *N,N*-dimethylglycyl acyl groups were synthesized with dioxaocta-3,5-diyne and with dioxaoctyl bridges (**7** and **8**), rigid molecules containing a hydrophobic pocket. Dynamic NMR spectroscopy revealed the presence of a conformational equilibrium between limiting syn and anti conformations. A water-soluble phane was observed by fluorescence and NMR spectroscopy to form inclusion complexes with 8-anilino-1-naphthalenesulfonic acid and with 2-naphthalenesulfonic acid having an association constant, in the case of 1,8-ANS, of 590 M^{-1}.

Introduction

Interest in water-soluble molecules containing a hydrophobic pocket as models of biological complexation has prompted us to prepare and study a number of [8.8](1,4)benzophanes[2] and [8.8](2,6)- and [8.8](1,4)naphthalenophanes.[3,4] Our results to date indicate that dioxaocta-3,5-diyne bridges as in **1** are effective in enforcing a rigid conformation in which the rings define a hydrophobic cavity ca. 3.6 Å (ring-ring distance of 7.2 Å) wide. When the diyne bridges are hydrogenated, NMR cyclization shifts (Δ_{cyc})[2,5] suggest that the rings collapse on each other with con-

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