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Conversion of Tetrahydroisoquinolinium Salts into Benzazepines

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Rearrangement of tetrahydroisoquinolinium salt **3** upon treatment with potassium *tert*-butoxide in *tert*-butyl alcohol gives benzazepine **5**. Similar treatment of salt **11** yields mostly cis benzazepine **13** together with a little trans **14**. In like fashion, a mixture of either trans and cis salts **21** and **22**, or of pure cis salt **22**, leads to a ≈3:1 mixture of trans benzazepine **23** and cis analogue **24**. Rearrangement of salt **25** supplies benzazepine **26**, whose O-methylation and air oxidation provides enamino ketone **28**. All these rearrangements proceed through quinone methide intermediates.

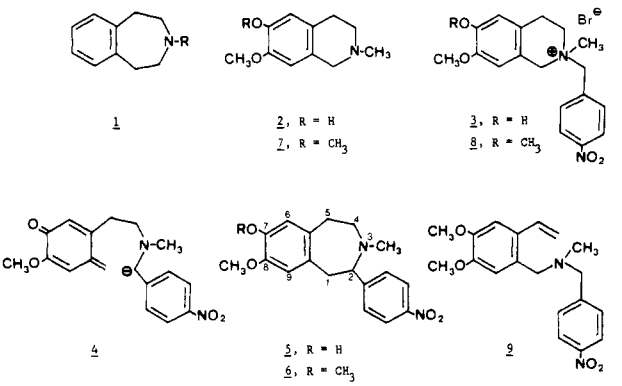
Substituted 3-benzazepines of type **1** (Chart I) have been reported to exhibit a variety of pharmacological activities, including hypotensive, hypoglycemic, analgesic, anoretic antibacterial, and antidepressant.[1,2] Additionally, the 3-benzazepine system, which in this paper will be referred to simply as benzazepine, is a skeletal feature of the rhoeadine, indenobenzazepine, isopavine, and cephalotaxine alkaloids.

With a view toward developing a new synthetic approach to the benzazepines, the general sequence depicted in Scheme I, which starts with a 6-hydroxylated tetrahydroisoquinoline salt and proceeds through the intermediacy of a quinone methide, seemed particularly attractive.

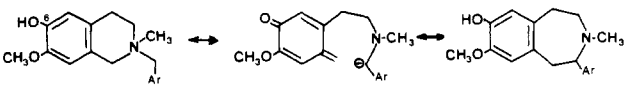
Quaternization of the known phenolic tetrahydroisoquinoline **2**[3,4] with *p*-nitrobenzyl bromide gave the corresponding salt **3** in 91% yield. Treatment of this salt with a little over 2 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol at 35 °C for 50 h afforded a 76% yield of the desired benzazepine **5** through the intermediacy of quinone methide **4**, which could be readily O-methylated to **6**.

Although the quinone methide mechanism for the formation of benzazepine **5** seemed plausible, the possibility of a Stevens rearrangement could not be discounted.[5] In order to eliminate such an alternate mechanism, the known 6,7-dimethoxy-*N*-methyltetrahydroisoquinoline **7**[6,7] was

Chart I



Scheme I



quaternized with *p*-nitrobenzyl bromide, and the resulting salt **8** was subjected to the same reaction conditions that had transformed salt **3** into benzazepine **5**. The one characterizable product in this case proved to be styrene **9**, so that a Stevens mechanism can be excluded from consideration.

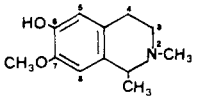
Attention was next directed toward the inclusion of C-1 substituents in the starting tetrahydroisoquinolines, which would eventually lead to benzazepines substituted at both C-1 and C-2. It has been shown by Bernâth and others that for 1-substituted tetrahydroisoquinolines, the preferred direction of attack for the quaternizing group is

(1) Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45–98.
(2) Pecherer, B.; Sunbury, R. C.; Brossi, A. *J. Heterocycl. Chem.* **1972**, 609. Some benzazepines also exhibit potent neuroleptic activity, see: Kaiser, C.; Ali, F. E.; Bondinell, W. E.; Brenner, M.; Holden, K. G.; Ku, T. W.; Oh, H.-J.; Ross, S. T.; Yim, N. C. F.; Zirkle, C. L.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Wardell, J. R. *J. Med. Chem.* **1980**, *23*, 975.
(3) Whaley, W. M.; Govindachari, T. R. *Org. React. (N.Y.)* **1951**, *6*, 74.
(4) Bobitt, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967**, *32*, 2225. See also: Gensler, W. J. *Org. React. (N.Y.)* **1951**, *6*, 191.
(5) For reviews on the Stevens rearrangement, see: Zimmerman, H. E. "Molecular Rearrangements"; deMayo, P., Ed.; Interscience: New York, 1963; Vol. I, pp 223–233.
(6) Buck, J. S. *J. Am. Chem. Soc.* **1934**, *56*, 1769.
(7) Smissman, E. E.; Reid, J. R.; Walsh, D. A.; Borchardt, R. T. *J. Med. Chem.* **1976**, *19*, 127.

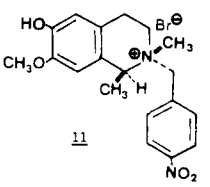
0022-3263/84/1949-0581$01.50/0

trans relative to the substituent at C-1.[8] For the *N*-methyl quaternary salts, the NMR signals for pseudoequatorial *N*-methyl groups appear further downfield than the corresponding pseudoaxial *N*-methyl signals.[8d] Furthermore, it is known that the methylene protons of a quaternary *N*-benzyl group are magnetically nonequivalent, with the extent of the nonequivalence magnified if the benzyl group experiences restricted rotation. On the one hand, if the *N*-benzyl group occupies a pseudoaxial position, its methylene protons usually appear as two distinct doublets, J_{gem} = 12–14 Hz. On the other hand, if this group is pseudoequatorial, the proton absorption in question takes the form of a singlet or a closely packed doublet of doublets.[9]

In the present study, quaternization of the known 1-methyl-substituted tetrahydroisoquinoline **10**[10] with *p*-nitrobenzyl bromide proved to be stereoselective, producing the trans salt **11** in 91% yield.

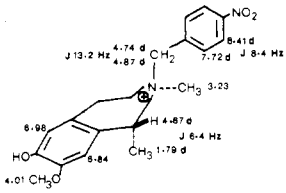


10

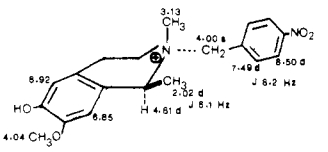


11

Examination of the NMR spectrum of salt **11** indicated the presence of two conformers in solution, dipseudoaxial (**11A**) and dipseudoequatorial (**11B**) in a 9:1 ratio. The



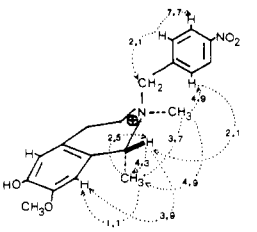
11A
H-3 and H-4:
3.34–3.88 (4 H, m)



11B
H-3 and H-4:
3.34–3.88 (4 H, m)

NMR chemical shifts have been summarized around expressions **11A** and **11B**, respectively. It will be noted that for conformation **11A**, the chemical shift for the pseudoaxial C-1 methyl doublet is relatively upfield at δ 1.79, while for conformation **11B** the corresponding doublet is further downfield at δ 2.02. Conversely, the pseudoequatorial *N*-methyl singlet in **11A** is more downfield (δ 3.23) than in **11B** (δ 3.13).

Further evidence for the pseudoaxial nature of the C-1 methyl and the *N*-*p*-nitrobenzyl groups in major conformation **11A** was forthcoming from NMR NOEDS (nuclear Overhauser enhancement difference studies).[11] The resulting data have been summarized around expression **11A(NOE)**. In particular, irradiation of the δ 7.72 absorption due to H-2′ and H-6′ led to a 2.1% NOE for H-1

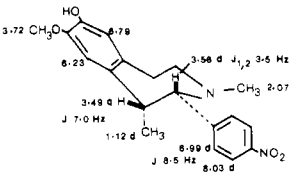


11A(NOE)

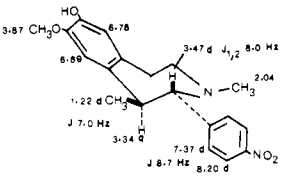
(δ 4.67), while no NOE was observed for the C-1 methyl doublet at δ 1.79.

Treatment of salt **11** with potassium *tert*-butoxide in *tert*-butyl alcohol afforded a separable mixture of cis benzazepine **13** and trans benzazepine **14** in 52% and 4% yields, respectively. Notable features in the NMR spectrum of the major cis isomer **13** (see expression **13-NMR**) are the pseudoaxial *C*-methyl doublet at δ 1.12 and the *N*-methyl singlet at δ 2.07. By irradiating the doublet at δ 1.12, the H-1 absorption was found to be a broad hump centered at δ 3.49, partially overlapping with the H-2 peak. The doublet at δ 3.56 representing H-2, with J = 3.5 Hz, is indicative of the cis configuration, with the C-1 methyl and the C-2 *p*-nitrophenyl at pseudoaxial and pseudoequatorial positions, respectively.[12]

By contrast, the NMR spectrum of the minor trans benzazepine **14** (**14-NMR**) exhibits a doublet at δ 1.22 for



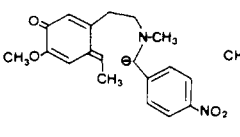
13-NMR
H-4 and H-5:
2.77–3.21 (4 H, m)



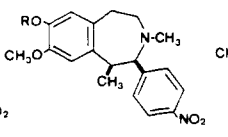
14-NMR
H-4 and H-5:
2.59–3.21 (4 H, m)

the *C*-methyl group and a singlet at δ 2.04 representing the *N*-methyl peak. H-1 is found at δ 3.34 as a slightly broadened quintet due to coupling associated with H-2 and the C-1 methyl protons. Irradiation of the C-1 methyl signal gave rise to a doublet replacing the quintet at δ 3.34. Most significantly, the H-2 doublet is found at δ 3.47 with $J_{1,2}$ = 8.0 Hz, indicating a trans configuration with dipseudoequatorial C-1 and C-2 substituents.

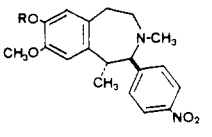
The stereochemistry in the almost exclusive formation of the cis isomer **13** can be explained by examination of the transition states leading to the formation of the cis and trans products. During the nucleophilic attack on the quinone methide terminal, tetrahedral-like character is being developed at the exo carbon of the quinone methide **12**. As bond-making and sp^3 character develop in this quinone methide, steric interactions arise between the methyl and *p*-nitrophenyl groups, which can be minimized through formation of the cis benzazepine **13**.



12



13, R = H
15, R = CH_3



14, R = H
16, R = CH_3

Reaction of cis **13**, contaminated with a little trans **14**, with diazomethane produced the separable isomeric benzazepines cis **15** and trans **16**. Salient resonances in the

(8) (a) Bernáth, G.; Kóbor, J.; Koczka, K.; Radics, L.; Kajtár, M. *Tetrahedron Lett.* **1968**, 225. (b) Bernáth, G.; Koczka, K.; Kóbor, J.; Radics, L.; Kajtár, M. *Acta Chim. Acad. Sci. Hung.* **1968**, *55*, 331. (c) Kóbor, J.; Bernáth, G.; Radics, L.; Kajtár, M. *Ibid.* **1969**, *60*, 225. (d) Radics, L.; Kajtár, M.; Kóbor, J.; Bernáth, G. *Ibid.* **1969**, *60*, 381. This cis–trans terminology refers to the stereochemical relationship between the larger substituent on the quaternary nitrogen and the substituent at C-1. (e) El-Sayad, H. A.; Swaringer, R. A.; Yeowell, D. A.; Crouch, R. C.; Hurlbert, S.; Miller, R. W.; McPhail, A. T.; Gross, P. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2067. (f) Wainer, I. W.; Sheinin, E. B. *J. Org. Chem.* **1982**, *47*, 1761.

(9) Whitesides, G. M.; Holtz, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2628. Horobin, R. W.; McKenna, J.; McKenna, J. M. *Tetrahedron, Suppl. 7*, **1966**, 35.

(10) Hoshino, O.; Ohyama, K.; Taga, M.; Umezawa, B. *Chem. Pharm. Bull.* **1974**, *22*, 2587.

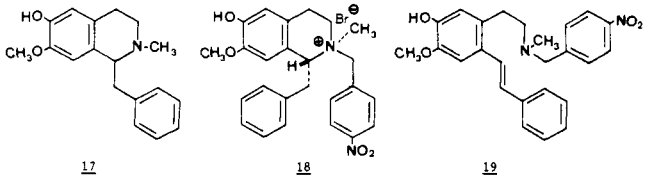
(11) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.

(12) Ibuka, T.; Konoshima, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23*, 133. Likforman, J.; Gardent, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *268*, 2340.

NMR spectrum of cis **15** consist of a doublet at δ 1.12 with J = 7 Hz for the C-1 methyl and another doublet at δ 3.55 with J = 3.5 Hz for H-2, indicating a cis configuration. Informative features in the spectrum of trans **16** are the C-1 methyl doublet at δ 1.24 with J = 7.0 Hz and the broadened quintet at δ 3.34 with J = 7.0 Hz for H-1. H-2 is observed as a doublet at δ 3.49 with J = 8.0 Hz.[12]

When cis **15** was heated at 80 °C with potassium *tert*-butoxide for 4 h, only the initial cis isomer could be detected by TLC. Attempted deuteration of cis **15** at C-2, using sodium methoxide in methanol-*d* at 35 °C for 72 h, failed to incorporate deuterium so that equilibration under the reaction conditions does not take place. Thus, the initially formed cis isomer **13** appears to be the kinetically favored product, although it could also be the thermodynamically preferred one.

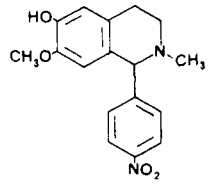
Our attention next turned to the quaternization of the known tetrahydrobenzylisoquinoline **17**[10] and the subsequent attempt at ring enlargement. Alkylation of **17** with



17 **18** **19**

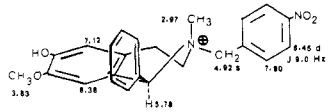
p-nitrobenzyl bromide in acetone at room temperature produced the trans quaternary salt **18** as a single diastereomer. Again, comparison of the *N*-methyl chemical shift (δ 3.52) with the corresponding Bernáth data (trans δ 3.43, cis 3.09) indicated we had on hand the trans isomer.[8d] Reaction of salt **18** with poassium *tert*-butoxide in *tert*-butyl alcohol at 35 °C for 29 h provided stilbene **19**, which is simply the Hofmann elimination product, while no benzazepine could be detected.

The next system to be investigated was the known 1-phenyltetrahydroisoquinoline **20**,[13] whose quaternization



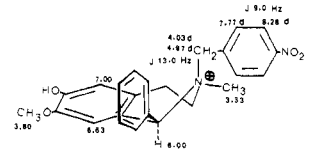
20

with *p*-nitrobenzyl bromide produced a mixture of trans salt **21** and cis salt **22** in a 2:1 ratio.



21

H-3 and H-4: δ 3.20–3.90 (4 H, m)
C-1 phenyl: δ 7.20–7.66 (5 H, m)



22

H-3 and H-4: δ 3.20–3.80 (4 H, m)
C-1 phenyl: δ 7.55 (5 H, s)

The *N*-methyl singlet for the trans salt **21** is at δ 2.97 (pseudoaxial) and that for cis salt **22** is at δ 3.33 (pseudoequatorial).[8d] The orientation of the bulky C-1 phenyl is pseudoequatorial in **21** as well as in **22**, so that the H-8 NMR absorption is always upfield, in the δ-6.38–6.63 range, due to shielding by the C-1 phenyl ring. The spectrum of the trans salt also displays a broad singlet for the benzylic methylene protons at δ 4.92, in contrast to the cis salt whose spectrum includes doublet resonances at δ 4.03 and 4.92 (J = 13.0 Hz) for the two benzylic protons. The existence of this doublet of doublets for cis salt **22** is due to the pseudoaxial orientation of the *p*-nitrobenzyl substituent and the restricted rotation of the methylene moiety. The C-1 and C-2 substituents are thus pseudodiequatorial in the trans isomer **21** and pseudoequatorial (C-1 phenyl) and pseudoaxial (C-2 *p*-nitrophenyl) in the cis isomer **22**.

Table I. NMR Chemical Shifts (δ) and NOE Data for Trans Benzazepine **23**

proton irradiated (δ)	proton observed (δ)	area increase, %
H-3″ and H-5″ (8.07)	H-2″ and H-6″ (7.28)	9.4
H-2′ to H-6′ (7.24)	H-3″ and H-5″ (8.07)	7.5
H-2″ and H-6″ (7.28)	H-9 (6.34)	4.2
	H-1 (4.53)	9.4
	H-2 (4.42)	10.9
H-9 (6.34)	H-2′ to H-6′ (7.24)	1.7
	H-1 (4.53)	4.7
	H-2 (4.42)	2.3
	C-8 OCH_3 (3.66)	4.7
H-1 (4.53)	H-2″ and H-6″ (7.28)	10.2
	H-2′ to H-6′ (7.24)	2.5
	H-9 (6.34)	9.7
H-2 (4.42)	H-2″ and H-6″ (7.28)	12.5
	H-2′ to H-6′ (7.24)	4.1
	H-9 (6.34)	4.9
	N-CH_3 (2.15)	1.1
C-8 OCH_3 (3.66)	H-9 (6.34)	16.2
NCH_3 (2.15)	H-2″ and H-6″ (7.28)	1.3
	H-2	7.0

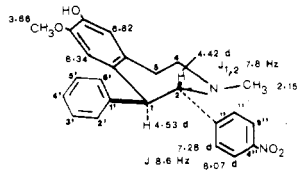
Slow recrystallization of the aforementioned predominantly trans mixture of salts from ethanol–ether produced the cis salt **22**, as well as a mixture of trans and cis salts. Cis salt **22** crystallized more readily than its trans analogue, thus assisting the isomerization of the trans to the cis compound. This epimerization is not unprecedented, since other *N*-benzyl quaternary salts are known to isomerize when heated.[8,14]

Reaction of trans **21** or cis **22** or the mixture of **21** and **22** with potassium *tert*-butoxide in *tert*-butyl alcohol supplied in each case trans benzazepine **23** in about 60% yield and *cis*-benzazepine **24** in ≃20% yield. The NMR chemical shifts for the trans and cis benzazepine products are outlined around expressions **23** and **24**. The results of an accompanying NOEDS are also presented in Tables I and II.

Trans benzazepine **23** exists predominantly in a conformation in which the bulky aryl and benzyl substituents at C-1 and C-2 are dipseudoequatorial. H-9 appears upfield at δ 6.34, being shielded by the C-1 phenyl ring. The coupling constant of 7.8 Hz between H-1 and H-2 implies a dihedral angle of about 170° (or 10°). Irradiation of H-1 (δ 4.53) produced 9.7% and 10.2% NOE's of H-9 (δ 6.34) and the H-2″ and H-6″ *p*-nitrophenyl absorption (δ 7.28), respectively, while the H-2 signal (δ 4.42) did not increase in size, indicating that H-1 and H-2 are facing in opposite directions. Similarly, irradiation of H-2 led to NOE's of 12.5%, 4.9%, and 1.1% for H-2″ and H-6″ (δ 7.28), H-9

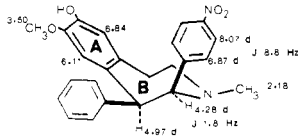
(13) Kametani, T.; Shio, M. *J. Heterocycl. Chem.* **1965**, *2*, 222.

(14) McKenna, J.; McKenna, J. M.; Tulley, A.; White, J. *J. Chem. Soc.* **1965**, 1711. Becconsall, J. K.; Jones, R. A. Y.; McKenna, J. *Ibid.* **1965**, 1726. Becconsall, J. K.; Jones, R. A. Y.; McKenna, J. *Ibid.* **1965**, 1729. McKenna, J.; McKenna, J. M.; White, J. *Ibid.* **1965**, 1733.



23

H-4 and H-5: δ 2.65-3.14 (4 H, m)
C-1 phenyl: δ 7.24 (5 H, m)



24

H-4 and H-5: δ 2.24-2.95 (4 H, m)
C-1 phenyl (H-3 to H-5): δ 7.25 (3 H, m)
C-1 phenyl (H-2 and H-6): δ 6.95 (2 H, m)

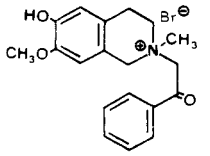
(δ 6.34), and the *N*-methyl signal (δ 2.15), while the H-1 signal (δ 4.53) remained unaffected.

Cis benzazepine **24**, on the other hand, exists in a preferred conformation in which H-1 is pseudoaxial but H-2 is pseudoequatorial. H-9 falls upfield at δ 6.11 since it is shielded by the C-1 phenyl ring. Similarly, the H-2″ and H-6″ signals of the *p*-nitrophenyl system are situated upfield at δ 6.87, again due to shielding by ring A. Significantly, H-1 and H-2 appear as broad unresolved doublets (with $J_{1,2}$ = 1.8 Hz), indicating a dihedral angle of about 80° between them. Irradiation of H-1 (δ 4.97) led to 10.1%, 3.5%, and 7.8% NOE's for the C-1 phenyl H-2′ and H-6′ (δ 6.95), H-9 (δ 6.11), and H-2 (δ 4.28) absorptions, respectively. Alternatively, irradiation of H-2′ and H-6′ caused NOE's of 8.3%, 9.7%, 12.5%, and 3.9% for the phenyl H-3′, H-4′ and H-5′ (δ 7.25), H-9, H-1 and H-2, respectively. Finally, irradiation of H-2 resulted in 10.9%, 11.1%, and 1.5% NOE's for H-1, H-2″ and H-6″, and the *N*-methyl (δ 2.18).

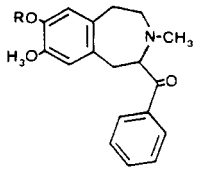
Furthermore, attempted equilibration of the trans and cis benzazepines **23** and **24** under our standard basic conditions, potassium *tert*-butoxide in *tert*-butyl alcohol, at 35 °C or at 80 °C, did not epimerize either isomer, thereby indicating that equilibration of the initially formed product does not occur under the reaction conditions employed. It is reasonable to conclude, therefore, that the trans/cis benzazepine ratio obtained is a function of the relative stabilities of the transition states involved.

Another conclusion derived from the above results is that C-1-substituted tetrahydroisoquinolinium salts supply C-1-substituted benzazepines, provided that the C-1 substituent in the starting salt has a minimal tendency toward Hofmann elimination.

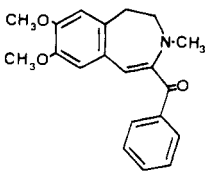
As an extension of the above findings, tetrahydroisoquinoline **2** was quaternized by using phenacyl bromide in acetonitrile to supply quaternary salt **25**. Reaction of **25** under our basic conditions supplied 2-benzoylbenzazepine **26**, which exhibits a yellow tinge due to air oxidation. O-Methylation with diazomethane led to dimethoxybenzazepine **27**. Air oxidation of **27** in basic solution provided orange crystalline enamino ketone **28** whose NMR spectrum displays the vinylic proton as a singlet at δ 6.10. Benzazepines substituted at C-2 can thus be prepared by treatment of properly substituted 6-hydroxylated tetrahydroisoquinoline salts with potassium *tert*-butoxide.



25



26, R = H
27, R = CH_3



28

Experimental Section

Standard Experimental Conditions. ^1H NMR spectra are at 200 or at 360 MHz. ^{13}C NMR chemical shifts values with identical superscripts are interchangeable. TLC was performed on Merck silica gel F-254 glass plates.

General Method A. Quaternization. To the tetrahydroisoquinoline dissolved in warm acetonitrile (12–18 mL/mmol) was added the alkylating agent (1.2 mole ratio) dissolved in acetonitrile (2–12 mL). The resulting mixture was refluxed (1–2 h) under nitrogen, cooled, and filtered, and the solid was dried at reduced pressure.

General Method B. Ring Expansion. After *tert*-butyl alcohol (≈250 mL/mmol of salt) was degassed at 35 °C for 1 h, the quaternary salt was suspended in this medium under a static nitrogen atmosphere. Generally, the mixture became yellow upon the addition of potassium *tert*-butoxide (2.5–3.0 mol/mol of salt). After being stirred until solution was achieved (3–50 h), the mixture was acidified with 3 N hydrochloric acid and the solvent evaporated. The residue was basified with ammonium hydroxide or sodium bicarbonate solution and the organic matter extracted with chloroform. The chloroform extracts were dried and stripped, and the residue was purified by either preparative TLC or recrystallization.

6-Hydroxy-7-methoxy-*N*-methyl-*N*-(*p*-nitrobenzyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (3). Following method A, 6-hydroxy-7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline[4] (**2**, 0.60 g, 3.10 mmol) in acetonitrile (55 mL) was quaternized with *p*-nitrobenzyl bromide (0.80 g, 3.72 mmol) in acetonitrile (10 mL), giving 1.16 g (91%); mp 208–214 °C dec. A sample recrystallized from acetonitrile had the following: mp 221–223.5 °C dec; NMR (TFA) δ 3.30 (s, 3 H, NCH_3), 3.20–3.50 (m, 2 H, H-4), 3.98 (s, 3 H, OCH_3), 3.80–4.10 (m, 2 H, H-3), 4.53 (d, 1 H, J_{gem} = 15 Hz, H-1a), 4.75 (d, 1 H, J_{gem} = 15 Hz, H-1b), 4.91 (br s, 2 H, NCH_2ArNO_2), 6.85 (s, 1 H, Ar H), 7.02 (s, 1 H, Ar H), 7.92 (d, J = 8.5 Hz, 2 H, H-2′ and -6′), and 8.48 (d, J = 8 Hz, 2 H, H-3′ and -5′).

An analytical sample was recrystallized from methanol; mp 158.5–162 °C dec. Anal. Calcd for $C_{18}H_{21}N_2O_4Br \cdot CH_3OH$: C, 51.71; H, 5.71; Br, 18.11. Found: C, 51.84; H, 5.73; Br, 18.45.

7-Hydroxy-8-methoxy-3-methyl-2-(*p*-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5). Using method B, reaction of quaternary salt **3** (0.30 g, 0.73 mmol) in *tert*-butyl alcohol (190 mL) with potassium *tert*-butoxide (0.21 g, 1.85 mmol) for 50 h gave, after recrystallization from ethanol, 0.17 g (69%); mp 163–164 °C. Another 0.017 g (7%) of product was obtained by preparative TLC of the mother liquor on silica gel, eluting with methanol–chloroform (3:97): R_f 0.33 in methanol–chloroform (5:95); λ_{max}^{EtOH} 211, 233 sh, 279 nm (log ε 4.17, 3.92, 4.03); NMR ($CDCl_3$) δ 2.05 (s, 3 H, NCH_3), 2.17–3.50 (m, 7 H, H-1, -2, -4, and -5), 3.80 (s, 3 H, OCH_3), 6.53 (s, 1 H, Ar H), 6.72 (s, 1 H, Ar H), 7.52 (d, J = 8.5 Hz, 2 H, H-2′ and -6′), and 8.17 (d, J = 8.5 Hz, 2 H, H-3′ and -5′); ^{13}C NMR ($CDCl_3$) δ 34.6 (t, C-5), 43.8 (t, C-1), 45.6 (q, NCH_3), 56.0 (q, OCH_3), 57.4 (t, C-4), 70.4 (d, C-2), 112.4[a] (d, C-9), 115.1[a] (d, C-6), 123.9 (d, C-3′ and -5′), 127.9 (d, C-2′ and -6′), 130.6[b] (s, C-5a), 134.8[b] (s, C-9a), 144.0[c] (s, C-1′), 144.4[c] (s, C-7), 146.9[c] (s, C-8), 153.4 (s, C-4′); MS, m/z (relative intensity) 328 (base) $(M)^+$, 272 (78), 177 (27), 164 (37), 151 (39).

An analytical sample was recrystallized from benzene; mp 164–165 °C. Anal. Calcd for $C_{18}H_{20}NO_4$: C, 65.84; H, 6.14. Found: C, 65.60; H, 6.14.

Table II. NMR Chemical Shifts (δ) and NOE Data for Cis Benzazepine 24

proton irradiated (δ)	proton observed (δ)	area increase, %
H-3'' and H-5'' (8.07)	H-2'' and H-6'' (6.87)	11.8
H-3' to H-5' (7.25)	H-2' and H-6' (6.95)	10.4
H-2' and H-6' (6.95)	H-3' to H-5' (7.25)	8.3
	H-9 (6.11)	9.7
	H-1 (4.97)	12.5
	H-2 (4.28)	3.9
H-2'' and H-6'' (6.87)	H-3'' and H-5'' (8.07)	23.6
	H-2 (4.28)	12.5
H-9 (6.11)	H-2' and H-6' (6.95)	4.9
	H-1 (4.97)	4.7
	C-8 OCH_3 (3.50)	4.5
H-1 (4.97)	H-2' and H-6' (6.95)	10.1
	H-9 (6.11)	3.5
	H-2 (4.28)	7.8
H-2 (4.28)	H-2'' and H-6'' (6.87)	11.1
	H-1 (4.97)	10.9
	N-CH_3 (2.18)	1.5
C-8 OCH_3 (3.50)	H-9 (6.11)	18.0
N-CH_3 (2.18)	H-2'' and H-6'' (6.87)	2.1
	H-2 (4.28)	12.8

6,7-Dimethoxy-*N*-methyl-*N*-(*p*-nitrobenzyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (8). 6,7-Dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (7) was obtained by basification of its hydrochloride salt[6,7] (0.70 g, 2.83 mmol) with ammonium hydroxide. Employing method A, alkylation of 7 in acetonitrile (5 mL) with *p*-nitrobenzyl bromide (0.75 g, 3.45 mmol) in acetonitrile (5 mL) followed by the addition of anhydrous ethyl ether (5 mL) to the hot solution gave 0.99 g (82%): mp 222–223 °C; NMR (TFA) δ 3.28 (s, 3 H, NCH_3), 3.40 (t, J = 6 Hz, 2 H, H-4), 3.98 (s, 6 H, 2 × OCH_3), 3.75–4.13 (m, 2 H, H-3), 4.52 (d, J = 15 Hz, 1 H, H-1a), 4.75 (d, J = 15 Hz, 1 H, H-1b), 4.90 (br s, 2 H, NCH_2ArNO_2), 6.85 (s, 1 H, Ar H), 6.98 (s, 1 H, Ar H), 7.90 (d, J = 8.5 Hz, 2 H, H-2' and -6'), 8.47 (d, J = 8.5 Hz, 2 H, H-3' and -5').

Reaction of 8 with Potassium *tert*-Butoxide. Following method B, salt 8 (0.20 g, 0.47 mmol) in *tert*-butyl alcohol alcohol (125 mL) was treated with potassium *tert*-butoxide (0.13 g, 1.16 mmol) for 3 h to give after solvent evaporation a black residue. Ethyl ether (25 mL) was added to the residue, which was filtered and then extracted with 5% hydrochloric acid. The acid extract was basified and extracted with ether. The amine mixture was separated by TLC using methanol–chloroform (5:95). The major band proved to be oily 9: 0.052 g (32%); λ_{max}^{EtOH} 215 and 266 nm (log ε 3.99 and 4.09); NMR ($CDCl_3$) δ 2.17 (s, 3 H, NCH_3), 3.55 (s, 4 H, $ArCH_2N$ and NCH_2ArNO_2), 3.87 (s, 6 H, 2 × OCH_3), 5.23 (d of d, J = 1.5, 11 Hz, 1 H, β-vinyl H), 5.55 (d of d, J = 1.5, 17 Hz, 1 H, β-vinyl H), 6.85 (s, 1 H, Ar H), 7.03 (s, 1 H, Ar H), 7.10 (d of d, J = 11, 17 Hz, 1 H, α-vinyl H), 7.47 (d, J = 9 Hz, 2 H, H-2' and -6'), and 8.12 (d, J = 9 Hz, 2 H, H-3' and -5'); MS, m/z (relative intensity) 342 (32) $(M)^+$, 313 (41), 206 (94), 177 (base), 146 (44); high-resolution MS calcd for $C_{19}H_{22}N_2O_4$ 342.1579, found 342.1577.

***trans*-6-Hydroxy-7-methoxy-1,2-dimethyl-2-(*p*-nitrobenzyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (11).** Utilizing method A, quaternization of 6-hydroxy-7-methoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (10)[10] (1.4 g, 6.75 mmol) in acetonitrile (80 mL) with *p*-nitrobenzyl bromide (1.82 g, 8.42 mmol) in acetonitrile (12 mL) gave 2.61 g (91%); mp 226–228 °C dec.

An analytical sample was recrystallized from methanol; mp 223–226 °C dec. Anal. Calcd for $C_{19}H_{23}N_2O_4Br$: C, 53.91; H, 5.48; Br, 18.88. Found: C, 54.00; H, 5.43; Br, 19.45.

***cis*- and *trans*-7-Hydroxy-8-methoxy-1,3-dimethyl-2-(*p*-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13 and 14).** Employing method B, salt 11 (0.60 g, 1.41 mmol) in *tert*-butyl alcohol (380 mL) was treated with potassium *tert*-butoxide (0.476 g, 4.24 mmol) for 43 h. After workup, several recrystallizations of the residue using ethanol provided two fractions. One fraction was pure cis isomer 13, while the other fraction was a cis/trans mixture. Isomeric purity was determined by TLC using a mixture of methanol–ethyl acetate (2:98) as solvent. The mixture was separated by using preparative TLC, eluting with the same solvent system.

13: 0.25 g (52%); mp 194–196 °C (EtOH); R_f 0.33; λ_{max}^{EtOH} 279 nm (log ε 3.95); MS, m/z (relative intensity) 342 (base) $(M)^+$, 286 (67), 178 (32), 177 (34), 165 (25), 164 (17), 163 (58).

An analytical sample was recrystallized from methanol; mp 195–196 °C. Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48. Found: C, 66.24; H, 6.77.

The higher component (R_f 0.47) of the cis/trans mixture after being washed from the silica gel by using chloroform, provided, upon solvent evaporation, 14: ca. 0.020 g (4%); mp 227.5–229.5 °C; MS, m/z (relative intensity) 342 (base) $(M)^+$, 286 (78), 178 (36), 177 (39), 165 (31), 164 (20), 163 (67); high-resolution MS calcd for $C_{19}H_{22}N_2O_4$ 342.1579, found, 342.1590.

***cis*- and *trans*-7,8-Dimethoxy-1,3-dimethyl-2-(*p*-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (15 and 16).** Diazomethane (5–7 mmol) in ether (100 mL) was added to a solution of cis benzazepine 13 (0.171 g, 0.499 mmol), slightly contaminated with the trans isomer 14, in a mixture of chloroform (30 mL) and methanol (30 mL), and the solution was stored in the freezer for 48 h. The crude mixture obtained after solvent evaporation was purified by TLC using methanol–chloroform (2:98). The higher of the two close bands (R_f 0.38) was further purified by TLC using methanol–ethyl acetate (2:98).

15: R_f 0.44 [methanol–ethyl acetate (2:98)]; oil, 0.148 g (83%); NMR ($CDCl_3$) δ 1.12 (d, J = 7 Hz, 3 H, C-1 CH_3), 2.10 (s, 3 H, NCH_3), 2.81–3.27 (m, 4 H, H-4 and -5), 3.50 (br, 1 H, H-1), 3.55 (d, J = 3.5 Hz, 1 H, H-2), 3.72 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.27 (s, 1 H, Ar H), 6.74 (s, 1 H, Ar H), 7.00 (m, 2 H, H-2' and -6'), 8.04 (d, J = 9 Hz, 2 H, H-3' and -5'); ^{13}C NMR ($CDCl_3$) δ 16.3 (q, C-1 CH_3), 33.7 (t, C-5), 40.5 (d, C-1), 45.4 (q, NCH_3), 52.4 (t, C-4), 55.8[a] (q, C-7 OCH_3), 56.1[a] (q, C-8 OCH_3), 74.1 (d, C-2), 111.0[b] (d, C-9), 112.8[b] (d, C-6), 122.4 (d, C-3' and -5'), 130.1 (d, C-2' and -6'), 132.0[c] (s, C-5a), 132.4[c] (s, C-9a), 146.7[d] (s, C-1'), 146.9[d] (s, C-8), 147.2[d] (s, C-7), 148.3 (s, C-4'); MS, m/z (relative intensity) 356 (93) $(M)^+$, 300 (base), 192 (16), 179 (19), 178 (24), 177 (54); high-resolution MS calcd for $C_{20}H_{24}N_2O_4$ 356.1735, found 356.1757.

The slightly less polar trans 16: R_f 0.44 [methanol–ethyl acetate (2:98)]; oil, 0.008 g (4%); NMR ($CDCl_3$) δ 1.24 (d, J = 7 Hz, 3 H, CH_3 C-1), 2.06 (s, 3 H, NCH_3), 2.54–2.67 (m, 1 H, H-5a), 2.83–3.24 (m, 3 H, H-4 and -5b), 3.34 (br quintet, $J \simeq 7$ Hz, 1 H, H-1), 3.49 (d, J = 7.7 Hz, 1 H, H-2), 3.87 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.72 (s, 1 H, Ar H), 6.74 (s, 1 H, Ar H), 7.37 (d, J = 7.5 Hz, 2 H, H-2' and -6'), 8.19 (d, J = 7.5 Hz, 2 H, H-3' and -5'); MS, m/z (relative intensity) 356 (74) $(M)^+$, 300 (base), 192 (23), 179 (35), 178 (28), 177 (78); high-resolution MS calcd for $C_{20}H_{24}N_2O_4$ 356.1735, found 356.1730.

Attempted Equilibration of Cis Benzazepine 15. Potassium *tert*-butoxide (59 mg, 0.53 mmol) was added to 15 (6 mg, 0.017 mmol) suspended in *tert*-butyl alcohol (14 mL). The resulting yellow solution was maintained in an 80 °C oil bath for 4 h under nitrogen. After being cooled, the solution was acidified with 10% hydrochloric acid and the solvent evaporated. The residue was basified with dilute ammonium hydroxide and extracted with chloroform. The chloroform extract was dried and the solvent evaporated. TLC indicated the presence of only the cis starting isomer.

Attempted Deuteration of Cis Benzazepine 15. Sodium methoxide (27 mg, 0.5 mmol) was added to 15 (18 mg, 0.051 mmol) dissolved in methanol-*d* (5 mL). After being maintained at 35 °C for 72 h under nitrogen, the solution was acidified with DCl–CH_3COOD–D_2O [acetyl chloride (0.02 mL) and deuterium oxide (1.8 mL)] and the solvent evaporated. The residue was basified with sodium bicarbonate and extracted with chloroform. The chloroform extract was washed with saturated sodium chloride and dried. Solvent evaporation gave 15 mg of 15. Mass spectrometry indicated no deuterium incorporation.

***trans*-1-Benzyl-6-hydroxy-7-methoxy-*N*-methyl-*N*-(*p*-nitrobenzyl)-1,2,3,4-tetrahydroisoquinolinium Bromide (18).** To 1-benzyl-6-hydroxy-7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline[10] (17, 0.80 g, 2.82 mmol) dissolved in acetone (115 mL) was added *p*-nitrobenzyl bromide (0.73 g, 3.39 mmol) in acetone (12 mL). Fine yellow crystals separated after 1 day and were filtered. A second crop was obtained following solvent evaporation to give a total yield of 1.32 g (94%); mp 154–156 °C.

Recrystallization of the crude product from acetonitrile provided 1.03 g (73%): mp 165–167 °C; NMR (TFA) δ 2.83–4.22 (m, 6 H, CH_2CH_2 and $ArCH_2$ C-1), 3.52 (s, 6 H, OCH_3 and NCH_3), 4.30–5.08 (m, 1 H, H-1), 4.93 (AB q, J = 13 Hz, 2 H, NCH_2ArNO_2), 5.83 (s, 1 H, H-8), 6.72–7.43 (m, 6 H, Ar H), 7.70 (d, J = 9 Hz, H-2′ and -6′), 8.40 (d, J = 9 Hz, H-3′ and -5′).

***trans*-4-Hydroxy-5-methoxy-2-[2-(*N*-methyl-*N*-*p*-nitrobenzylamino)ethyl]stilbene (19).** Following method B, treatment of salt **18** (0.27 g, 0.54 mmol) in *tert*-butyl alcohol (180 mL) with potassium *tert*-butoxide (0.18 g, 1.60 mmol) for 29 h gave, after workup, 0.19 g of a mixture. Further purification of this mixture (0.051 g) by TLC, eluting with ether saturated with ammonium hydroxide, provided stilbene **19**: 0.032 g, mp 90–93 °C (acetone); λ_{max}^{EtOH} 244, 293, and 329 nm (log ε 4.05, 4.16, and 4.17); MS, m/z (relative intensity) 418 (10) $(M)^+$, 179 (base), 136 (14); high-resolution MS calcd for $C_{25}H_{26}N_2O_4$ 418.1892, found 418.1910.

***cis*- and *trans*-6-Hydroxy-7-methoxy-*N*-methyl-*N*-(*p*-nitrobenzyl)-1-phenyl-1,2,3,4-tetrahydroisoquinolinium Bromide (22 and 21).** To **20**[13] (0.50 g, 1.86 mmol) dissolved in warm acetonitrile (15 mL) was added a solution of *p*-nitrobenzyl bromide (0.48 g, 2.22 mmol) in acetonitrile (5 mL), and the solution was refluxed under nitrogen for 1.5 h. The solvent was evaporated, and the residue was washed with anhydrous ether to give a mixture of **22** and **21**, 0.89 g (99%). A small sample was purified by TLC using methanol–chloroform (15:85). Two diastereomeric salts could be distinguished by the NMR spectrum. The NMR spectra of both the crude and the purified salts displayed a trans to cis isomer ratio of about 2:1.

The quaternization was repeated with twice the amount of all reagents and solvent, with refluxing for 1.5 h. After workup, the crude salts were recrystallized from ethanol–ether to obtain relatively pure cis **22**: 1.33 g (74%), mp 167–171 °C dec. Evaporation of the mother liquors provided a mixture of cis and trans isomers, 0.41 g (23%), mp 161–168 °C, ca. cis 44% and trans 56%.

An analytical sample of **22** was recrystallized from ethanol–ether: mp 164–167 °C dec. Anal. Calcd for $C_{24}H_{25}N_2O_4Br \cdot 1.5C_2H_5OH$: C, 58.47; H, 6.18; Br, 14.41. Found: C, 57.97; H, 6.04; Br, 15.32.

***trans*- and *cis*-7-Hydroxy-8-methoxy-3-methyl-2-(*p*-nitrophenyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (23 and 24).** The recrystallized cis salt **22** was dissolved in acetonitrile, the solvent evaporated, and the residue dried in vacuo to remove entrapped ethanol. Following method B, the salt (0.14 g, 0.3 mmol) in *tert*-butyl alcohol (80 mL) was treated with potassium *tert*-butoxide (0.10 g, 0.89 mmol) for 18 h. Purification by TLC, eluting with ethyl acetate, gave two amines.

The higher component (R_f 0.63), trans **23**, was obtained as a cluster of needles from ethanol: 0.073 g (61%); mp 184–185 °C; MS, m/z (relative intensity) 404 (base) $(M)^+$, 348 (25), 313 (94), 240 (20), 239 (26), 225 (47), 177 (41); high-resolution MS calcd for $C_{24}H_{24}N_2O_4$ 404.1734, found 404.1706.

The lower component (R_f 0.46), cis **24**: 0.026 g (22%); mp 193–194 °C (benzene); MS, m/z (relative intensity) 404 (base) $(M)^+$, 348 (21), 313 (92), 240 (3), 239 (30), 225 (46), 177 (36); high-resolution MS calcd for $C_{24}H_{24}N_2O_4$ 404.1734, found 404.1712.

Repeating the above reaction using the crude salt (trans/cis ratio 2:1) gave rise to the same yield and isomer ratio.

Attempted Equilibration of Cis 24 and Trans 23. Cis **24** and trans **23** were treated similarly. To the benzazepine (11 mg, 0.027 mmol) in a dry flask under nitrogen in a 35–40 °C oil bath was added dry *tert*-butyl alcohol (12 mL). Following addition of potassium *tert*-butoxide (37 mg, 0.330 mmol), the clear slurry became a yellow solution. After being stirred for 72 h, the solution was acidified by dilute hydrochloric acid and the solvent evaporated. The residue was basified with sodium bicarbonate solution and extracted with chloroform. The chloroform extract was dried and the solvent evaporated. TLC of the residue on silica gel using ethyl acetate indicated the presence of only the starting compound. The same result was obtained at 75–80 °C for 2 h instead of at 35–40 °C.

6-Hydroxy-7-methoxy-*N*-methyl-*N*-phenacyl-1,2,3,4-tetrahydroisoquinolinium Bromide (25). Following method A, alkylation of tetrahydroisoquinoline **2** (0.40 g, 2.07 mmol) in acetonitrile (30 mL) with phenacyl bromide (0.50 g, 2.51 mmol) in acetonitrile (2 mL) for 1.5 h gave a white solid: 0.68 g (84%); mp 208–210 °C dec; NMR (TFA) δ 3.27 (t, J = 6 Hz, 2 H, H-4), 3.68 (s, 3 H, NCH_3), 4.02 (s, 3 H, OCH_3), 4.00–4.70 (m, 2 H, H-3), 5.00 (AB q, J = 15 Hz, 2 H, H-1), 5.27 (s, 2 H, NCH_2COPh), 6.95 (s, 1 H, Ar H), 7.03 (s, 1 H, Ar H), 7.50–7.90 (m, 3 H, Ar H), 7.90–8.30 (m, 2 H, Ar H).

The analytical sample was recrystallized from acetonitrile; mp 198–200 °C dec. Anal. Calcd for $C_{19}H_{22}NO_3Br$: C, 58.17; H, 5.65; Br, 20.37. Found: C, 58.20; H, 5.77; Br, 20.55.

2-Benzoyl-7-hydroxy-8-methoxy-3-methyl-2,3,4,5-1*H*-3-benzazepine (26). Employing method B, quaternary salt **25** (0.32 g, 0.8 mmol) in *tert*-butyl alcohol (200 mL) was treated with potassium *tert*-butoxide (0.24 g, 2.14 mmol) for 3 h at 75–85 °C. Purification by TLC using methanol–chloroform (10:90) gave 0.19 g (76%): mp 121–124 °C (benzene); NMR ($CDCl_3$) δ 2.40 (s, 3 H, NCH_3), 2.60–3.60 (m, 6 H, H-1, -4, and -5), 3.78 (s, 3 H, OCH_3), 4.12 (d of d, J = 2, 8 Hz, 1 H, H-2), 5.37 (s, 1 H, Ar OH), 6.48 (s, 1 H, Ar H), 6.78 (s, 1 H, Ar H), 7.40–7.70 (m, 3 H, Ar H), 8.10–8.35 (m, 2 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 33.7 (t, C-5), 36.7 (t, C-1), 42.5 (q, NCH_3), 55.6 (t, C-4), 55.9 (q, OCH_3), 69.2 (d, C-2), 112.2 (d, C-9), 115.6 (d, C-6), 128.4 (d, C-3′ and C-5′), 128.6 (d, C-2′ and C-6′), 130.1[a] (s, C-5a), 133.0 (d, C-4′), 134.9[a] (s, C-9a), 136.1 (s, C-1′), 143.9[b] (s, C-7), 144.4[b] (s, C-8), 200.3 (s, C-7′); MS m/z (relative intensity) 311 (0.2) $(M)^+$, 310 (0.6), 309 (2), 206 (base), 191 (5), 105 (6); high-resolution MS calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1498.

2-Benzoyl-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (27). A solution of diazomethane (0.8 mmol) in ether (15 mL) and benzazepine **26** (0.10 g, 0.32 mmol) in methanol (20 mL) was stored in a freezer for 48 h. Workup included extraction with sodium hydroxide, and TLC and gave 0.066 g: mp 141–144 °C (methanol); $\nu_{max}^{CHCl_3}$ 1685 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3 H, NCH_3), 2.50–3.70 (m, 6 H, H-1, -4, and -5), 3.80 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.17 (d of d, J = 2, 9 Hz, 1 H, H-2), 6.53 (s, 1 H, Ar H), 6.77 (s, 1 H, Ar H), 7.40–7.75 (m, 3 H, Ar H), 8.05–8.30 (m, 2 H, Ar H); MS, m/z (relative intensity) 325 (0.4) $(M)^+$, 220 (base), 105 (3); high-resolution MS calcd for $C_{20}H_{23}NO_3$ 325.1677, found 325.1672.

2-Benzoyl-7,8-dimethoxy-3-methyl-4,5-dihydro-3*H*-3-benzazepine (28). A solution of benzazepine **27** (0.08 g, 0.25 mmol) in methanol (30 mL) and 10% sodium hydroxide (10 mL) was stirred for 2 days. Basicity was maintained by further addition of 10% sodium hydroxide. The methanol was evaporated, water added, and the mixture extracted with chloroform. The chloroform solution was dried and evaporated. The residue was purified by TLC using methanol–chloroform (5:95) to give 0.054 g (68%), mp 108–109 °C (methanol) as orange crystals. Also, 0.010 g of starting material was recovered. The yield of product was 77% based on consumed starting material: $\nu_{max}^{CHCl_3}$ 1645 cm^{-1}; I_{max}^{EtOH} 259, 290, and 388 nm (log ε 3.72, 3.70, and 3.87); NMR ($CDCl_3$) δ 2.67 (s, 3 H, NCH_3), 3.00 (m, 2 H, H-5), 3.30 (m, 2 H, H-4), 3.87 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.10 (s, 1 H, H-1), 6.80 (s, 2 H, Ar H), 7.55 (m, 3 H, Ar H), 8.05 (m, 2 H, Ar H); MS, m/z 323 (relative intensity) (base) $(M)^+$, 308 (34), 104 (34).

An analytical sample was recrystallized from methanol; mp 133–134 °C. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found: C, 74.27; H, 6.55.

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