butyl phthalate) as plasticizers in medically used devices, the question arises as to the potential danger to the human reproductive process from plasticizers leached from these devices by blood or parenteral solutions. While the doses of di-2-ethylhexyl phthalate employed in this study were greatly in excess of the 5–7 mg. % which have been reported in whole blood stored in di-2-ethylhexyl phthalate-plasticized blood bags (3), the possible cumulative nature of the plasticizer in the body must also be considered. Jaeger and Rubin (3) found from 2.5 to 27 mg. % (dry weight) of this plasticizer in tissues of patients who were known to have received blood transfusions; in addition, they found that while the perfused rat liver could hydrolyze the plasticizer butyl glycolylbutyl phthalate, it did not hydrolyze di-2-ethylhexyl phthalate but tended to sequester and accumulate it.

Further investigations are needed to determine the fate of these small, but possibly repeated, quantities of plasticizers that may enter the patient as a result of medical or surgical treatment and to determine what, if any, effect on reproduction or other physiological processes may result.

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Synthesis and NMR Spectral Characteristics of Bisnorargemonine Isomers

CHUNG-HSIUNG CHEN* and T. O. SOINE▲

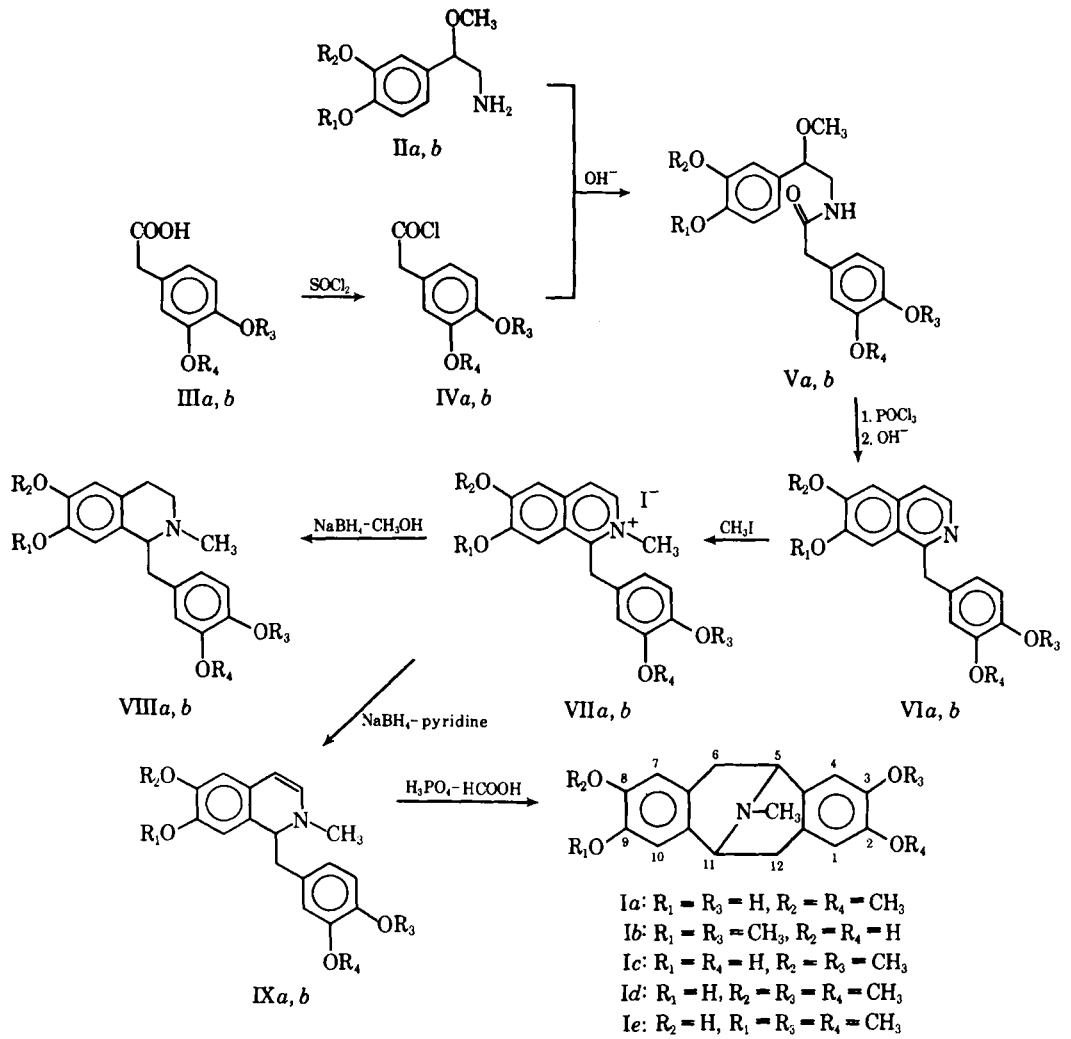
Abstract □ Two structural isomers of bisnorargemonine, 3,9-dihydroxy-2,8-dimethoxy-*N*-methylpavinane (I*a*) and 2,8-dihydroxy-3,9-dimethoxy-*N*-methylpavinane (I*b*), were synthesized employing the Pictet–Gams modification of the Bischler–Napieralski cyclization to construct the required isoquinoline intermediates. These were quaternized to the methiodides, followed by partial reduction to the *N*-methyl-1,2-dihydroisoquinolines, which were then cyclized under acidic conditions to provide I*a* and I*b*. Comparison of the NMR spectra of I*a* and I*b* with similar compounds revealed interesting aspects of the spectral properties pertaining to this ring system.

Keyphrases □ Bisnorargemonine isomers—synthesis, NMR characteristics □ 3,9-Dihydroxy-2,8-dimethoxy-*N*-methylpavinane—synthesis, NMR characteristics □ 2,8-Dihydroxy-3,9-dimethoxy-*N*-methylpavinane—synthesis, NMR characteristics □ NMR spectroscopy—characteristics of bisnorargemonine isomers

The recent synthesis of (±)-bisnorargemonine (1, 2) confirmed Structure I*c* assigned to it previously on the basis of its unique NMR spectrum (3). Two alternate structures, I*a* and I*b*, could have been considered but were rejected due to a predictable nonconformity in their NMR spectra. However, it was of interest to synthesize I*a* and I*b*, not only to verify the predicted NMR patterns but also to seek a practical synthetic route to provide these phenolic bases for projected oxidative coupling studies. The incidental provision of spectral and other data could also be of value in the future in assigning structures in the event that either or both of these diphenols are found to be naturally occurring, a not unlikely possibility.

Pursuant to a suggestion by Stermitz[1], it is believed appropriate to introduce a new type of nomenclature for this ring system since further extension of the "argemonine" nomenclature seems inadvisable if not impossible. Accordingly, it is proposed that the term "pav-

[1] Private communication from Dr. F. Stermitz, Colorado State University, Fort Collins, Colo., which forms the basis for the proposed nomenclature.



Scheme I—For Compounds II → IX: a, $R_1 = R_3 = CH_2Ph$, $R_2 = R_4 = CH_3$; *and* b, $R_1 = R_3 = CH_3$, $R_2 = R_4 = CH_2Ph$ (*Ph = phenyl here and in all tables*)

inane" with the numbering indicated in I be adopted for the tetracyclic ring system characteristic of these alkaloids. Under this system, I*a* would be 3,9-dihydroxy-2,8-dimethoxy-*N*-methylpavinane, I*b* would be 2,8-dihydroxy-3,9-dimethoxy-*N*-methylpavinane, and I*c* would be 2,9-dihydroxy-3,8-dimethoxy-*N*-methylpavinane. Other related alkaloids such as norargemonine (I*d*) and isonorargemonine (I*e*) would be handled accordingly and acquire the names 9-hydroxy-2,3,8-trimethoxy-*N*-methylpavinane and 8-hydroxy-2,3,9-trimethoxy-*N*-methylpavinane, respectively.

DISCUSSION

The synthesis of I*a* and I*b* followed, essentially, the procedures developed for synthesis of I*c* (1, 2). Scheme I outlines the key steps leading to I*a* and I*b*.

The initially required amines, II*a* and II*b*, were prepared as previously described (1, 2) by the method of Rosenmund *et al.* (4); the phenylacetic acids, III*a* and III*b*, were prepared by the methods of Douglas and Gulland (5) and Robinson and Sugasawa (6), respectively. Condensations between II*a* and IV*a* and between II*b* and IV*b* provided the respective amides, V*a* and V*b*, which were readily aromatized to the isoquinolines, VI*a* and VI*b*, by treatment with phosphorus oxychloride utilizing the Pictet–Gams variation of the Bischler–Napieralski cyclization (7). Quaternization of VI*a* and VI*b* with methyl iodide yielded VII*a* and VII*b*. To establish the structures of intermediates involved in this sequence, VII*a* and VII*b* were reduced with sodium borohydride in methanol to the known *N*-methyl-1,2,3,4-tetrahydroisoquinolines, VIII*a* and VIII*b*, the physical constants of which agreed with those synthesized by others (8, 9) *via* independent routes. Finally, partial reduction of VII*a* and VII*b* to the respective *N*-methyl-1,2-dihydroisoquinolines, IX*a* and IX*b*, by the sodium borohydride–pyridine method of Barton *et al.* (10) was followed by the acid-catalyzed cyclization of Battersby and Binks (11), which simultaneously cleaved the protective benzyloxy groups to give the desired diphenols, I*a* and I*b*.

Table I gives the NMR data for all the intermediate compounds involved in the synthetic scheme. Assignments of each signal were made by comparison with similar series of compounds prepared previously in the synthesis of I*c* (2). Other physical data (*i.e.*, UV and IR; see *Experimental* section) are also in keeping with the structures expected.

Combined column chromatography and preparative TLC were employed to isolate I*a* and I*b* from the reaction mixtures in 12 and 9% yields, respectively.

Both I*a* and I*b* showed in their mass spectra a molecular ion at *m/e* 327, which has an elemental composition of $C_{19}H_{21}NO_4$ as revealed by corresponding high-resolution mass spectra[2]. The IR absorption of I*a* at 3481 cm.$^{-1}$ and that of I*b* at 3480 cm.$^{-1}$ confirmed the phenolic functions in these molecules. That both compounds are indeed 2,3,8,9-tetrasubstituted *N*-methylpavinanes

[2] The authors are indebted to Dr. Gene Sparrow, Central Research Laboratories, Minnesota Mining and Manufacturing Co., St. Paul, Minn., for these spectra. They were carried out on a CEC model 21-110C high-resolution mass spectrometer.

Table I—NMR data[a] for V*a*, V*b*, VI*a*, VI*b*, VII*a*, VII*b*, IX*a*, and IX*b*

	OCH_3	OCH_2Ph	$-C(=O)-CH_2-$	β-OCH_3
V*a*	6.13(s, 6H)	4.85(s, 4H)	6.51(s)	6.83(s)
V*b*	6.09(s, 6H)	4.84(s, 4H)	6.55(s)	6.89(s)

	OCH_3				OCH_2Ph				C_1-CH_2	C_3-H
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'		
VI*a*	6.02	—	6.23	—	—	4.84	—	4.90	5.56(s)	1.60(d, $J_{3,4}$ = 6 Hz.)
VI*b*	—	6.14	—	6.14	4.70	—	4.95	—	5.47(s)	1.65(d, $J_{3,4}$ = 5.7 Hz.)

	OCH_3				OCH_2Ph				C_1-CH_2	C_3-H and C_4-H *AB* quartet	$\overset{+}{N}-CH_3$
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'			
VII*a*	5.87	—	6.17	—	—	4.67	—	4.92	4.96(s)	1.31, 1.72($J_{3,4}$ = 6.8 Hz.)	5.52(s)
VII*b*	—	6.02	—	6.23	4.51	—	4.94	—	4.96(s)	1.40, 1.69($J_{3,4}$ = 6.2 Hz.)	5.70(s)

	OCH_3				OCH_2Ph				C_1-H	C_3-H(d of d) and C_4-H(d)	$N-CH_3$	C_8-H
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'				
IX*a*	6.24	—	6.29	—	—	5.07	—	4.87	5.51(t)	3.84, 4.54($J_{3,4}$ = 7.2 Hz., $J_{1,3}$ = 1.2 Hz.)	7.21(s)	3.64(s)
IX*b*	—	6.39	—	6.23	4.86	—	4.91	—	5.54(t)	3.92, 4.57($J_{3,4}$ = 7.3 Hz., $J_{1,3}$ = 1.2 Hz.)	7.23(s)	3.74(s)

[a] Chemical shifts are given as τ values. Compounds V*a*, V*b*, VI*a*, VI*b*, and VII*a* were taken in $CDCl_3$; VII*b* was taken in dimethyl sulfoxide-d_6; and IX*a* and IX*b* were taken in pyridine-d_5.

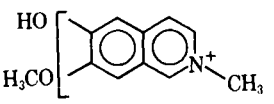
was shown by the characteristic "triplet" absorption bands in their UV spectra. Thus, I*a* absorbs at 285, 289, and 293 nm. and I*b* absorbs at 285, 289, and 294 nm., both being very similar to those of the *Argemone* alkaloids (12). This is further substantiated by comparison of the mass spectra of I*a* and I*b* with that of I*c* (Table II). The major mode of fragmentation was the formation of the *N*-methylisoquinolinium ion (X) (*m/e* 190) from the molecular ion (*m/e* 327), a fragmentation pattern characteristic of the ring system under consideration (13, 14). Upon close inspection, I*a*–I*c* showed a strong resemblance with respect to other minor ions, suggesting that the disposition of hydroxy and methoxy groups does not significantly affect the fragmentation pattern of these isomeric diphenols.

Examination of the NMR spectra of I*a* and I*b* (Table III) reveals the symmetrical nature of these two molecules. The aromatic protons are paired into two singlets, suggesting that H_1 is identical with H_7 in chemical environment as is H_4 with H_{10}. Similarly, the two methoxy groups are identical, and only one singlet of six protons was observed. Thus, all evidence points to Structures I*a* and I*b* for the compounds synthesized.

After these two structural isomers of bisnorargemonine (I*c*) were available, several interesting points began to emerge on comparison of their NMR spectra with those of other known compounds in the same series such as norargemonine (I*d*), isonorargemonine (I*e*), argemonine (I*f*), and 2,3,8,9-tetrahydroxy-*N*-methylpavinane (I*g*). Compound I*g* was originally prepared by demethylation of I*c* (15) and isolated as its hydrochloride salt. By employing the same procedure, demethylation of I*f* (see *Experimental*) provided the hydrochloride of I*g*, which was identical with the sample obtained from I*c* (15). Since the free base form of I*g* was rather unstable, the dimethyl sulfoxide-d_6 solution of the hydrochloride salt in an NMR tube was neutralized directly by incremental addition of NaOD in D_2O, and the change in chemical shifts was observed. As illustrated in Fig. 1, the chemical shifts of aromatic protons and *N*-methyl protons could be easily estimated at the point of neutralization because a maximum upfield shift of the *N*-methyl signal was reached. The values estimated in this manner are given in Table III.

For all compounds listed in Table III, the singlet for the *N*-methyl protons centers around τ 7.65 for all practical purposes. This is probably due to the fact that the *N*-methyl group is rather isolated from the rest of the molecule (*i.e.*, aromatic rings) where significant structural changes take place.

By taking I*a* and I*b* as reference compounds, it is possible to assign the chemical shift for each methoxy group at different positions on the ring. The methoxy groups at the C_2 and C_8 positions appear upfield by about 0.07–0.10 p.p.m. as compared to those at C_3 and C_9. This may be rationalized as being due to the inductive effect of the C—N bond at the bridge-head, which is nearer to the methoxy groups at C_3, C_9 than those at C_2, C_8.



X *m/e* 190

The most interesting chemical shifts, however, are those of the aromatic protons. Since I*a*, I*b*, I*f*, and I*g* all possess a twofold axis of symmetry, the aromatic protons are paired into two singlets. If one assumes that the inductive effect of a bridge-head C—N bond influences the chemical shifts of aromatic protons, then H_4 and H_{10} should be assigned to the low field singlet and H_1 and H_7 to the high field singlet. Furthermore, since the two aromatic rings in this type of structure are essentially independent of one another with respect to spin systems affecting NMR chemical shifts, a predictable additivity of spectra is observed. Thus, the spectrum of I*c* could be considered as a combination of I*a* and I*b*, I*d* as a combination of I*a* and I*f*, and I*e* as a combination of I*b* and I*f* (Fig. 2). Another consequence of this additive phenomenon is reflected in the constant range of upfield shift of a proton *ortho* to a hydroxyl group and a proton *meta* to a hydroxyl group if one takes the tetramethoxy Compound I*f* as a reference standard. As shown in Table IV, protons *ortho* to a hydroxyl group invariably undergo a greater upfield shift than do protons *meta* to a hydroxyl group. In Compound I*g*, the combined effect of *ortho* and *meta* upfield shifts is observed, and the observed values (0.25 and 0.29) agree quite well with the calculated value (0.26). Since both ranges of upfield shifts do not overlap, one could also take this as a criterion and thus make assignments for each aromatic proton. The results obtained are essentially the same as those listed in Table III.

The assumption was made in all the previous assignments that the inductive effect of a bridge-head C—N bond determined the chemical shift of the aromatic protons in the pavinane ring system. To confirm this, both I*a* and I*b* were incrementally converted into phenolate anions with NaOD and, at the same time, the change in chemical shift of the aromatic protons was observed (Fig. 3). I*f*, without phenolic hydroxyl groups, served as a reference compound to compensate for solvent effects on chemical shifts.

Highet and Highet (16) established that, on conversion to phenolate ions, the ensuing resonance effect generally causes the aromatic

Table II—Mass Spectra of I*a*–I*c*[a]

	m/e											
	327	190	328	326	312	311	191	177	176	175	162	137
I*a*	40	100	17	34	7	7	16	—	—	7	—	6
I*b*	30	100	7	25	6	5	15	—	—	8	—	6
I*c*	70	100	15	57	11	9	37	7	6	15	7	6

[a] Relative abundance of ions larger than 5%.

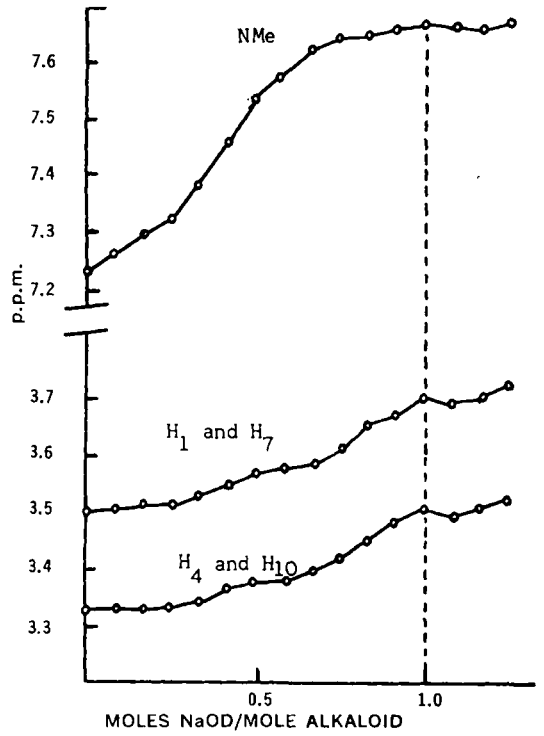


Figure 1—*Estimation for the chemical shifts of the N—Me group and aromatic protons of* Ig. *Gradual addition of NaOD in D_2O to the hydrochloride salt of* Ig *in dimethyl sulfoxide-*d_6.

protons to undergo an upfield shift, the range of upfield shift being greater for protons *ortho* to the hydroxy function than for protons *meta* to the hydroxy function. Based upon this, it is evident that the low field aromatic singlet in I*a*, which shifted upfield with a greater range, should, therefore, belong to protons *ortho* to the phenolic function, *i.e.*, H_4 and H_{10}. In I*b*, the high field singlet shifted with a greater range and hence is assigned to H_1 and H_7 which are *ortho* to phenolic groups. In both I*a* and I*b*, the low field singlet belongs to H_4 and H_{10} which are adjacent to a C—N bridge-head. This firmly establishes the validity of the assumption made previously that assignments of *ortho*- or *meta*-positions of aromatic protons in this system can be made without resort to conversion to the phenolate form.

Stermitz and Seiber (13) previously constructed similar curves for Ic–Ie. Once again, additivity was observed since the curve for Ic is a composite of I*a* and I*b*, Id is a composite of I*a* and I*f*, and Ie is a composite of I*b* and I*f*.

EXPERIMENTAL[3]

***N*-(3′-Methoxy-4′-benzyloxyphenylacetyl)-β-methoxy-β-(3-methoxy-4-benzyloxyphenyl)ethylamine (V*a*)**—A mixture of 8.50 g. (0.031 mole) of 3-methoxy-4-benzyloxyphenylacetic acid (III*a*) and 20 ml. of thionyl chloride in 150 ml. of chloroform was refluxed for 2 hr. The reaction mixture was concentrated, and the excess thionyl chloride was removed by repeated addition and evaporation of anhydrous toluene under vacuum. The oily acid chloride (IV*a*) was dissolved in 40 ml. of anhydrous benzene and added dropwise to a cooled (ice bath) and stirred mixture of 60 ml. of 10% NaOH and 8.97 g. (0.031 mole) of β-methoxy-β-(4-benzyloxy-3-methoxyphenyl)ethylamine (II*a*) (2) in 60 ml. of benzene. After the addition was completed, the stirring was continued overnight at room temperature. The benzene layer was then separated from the aqueous layer, and the latter was extracted twice with fresh benzene. The combined benzene solution was dried (anhydrous K_2CO_3) and evaporated to give a brown oil. This oil (about 15.8 g.) was further purified by passing through a silica gel column (350 g., Baker 3405, 60–200 mesh), using benzene–ethyl acetate (20:5) as the eluting solvent (100 ml./fraction). Fractions 18–25 were combined and evaporated to give a colorless oil, which crystallized from absolute ethanol to yield 13.30 g. (79%) of V*a* as white needles, m.p. 95.5–97°; IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 3322 (NH), 1639 (amide I), and 1507 (amide II).

Anal.—Calc. for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 72.97; H, 6.33; N, 2.33.

***N*-(3′-Benzyloxy-4′-methoxyphenylacetyl)-β-methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (V*b*)**—3-Benzyloxy-4-methoxyphenylacetic acid (III*b*) (13.82 g., 0.0508 mole) was converted to its acid chloride (IV*b*) and condensed with 0.0508 mole (from 16.87 g. oxalate salt) of β-methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (II*b*) (2) as already described. The crude product mainly precipitated directly from the reaction mixture, but some was also obtained from the organic layer. The combined product was crystallized from 95% ethanol to yield 74% of V*b*. Recrystallization from the same solvent gave fine white needles, m.p. 102.5–104.5°; IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 3324 (NH), 1635 (amide I), and 1510 (amide II).

Anal.—Calc. for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 73.11; H, 6.30; N, 2.56.

1-(3′-Methoxy-4′-benzyloxybenzyl)-6-methoxy-7-benzyloxyisoquinoline (VI*a*)—A mixture of 12.00 g. (0.022 mole) of V*a*

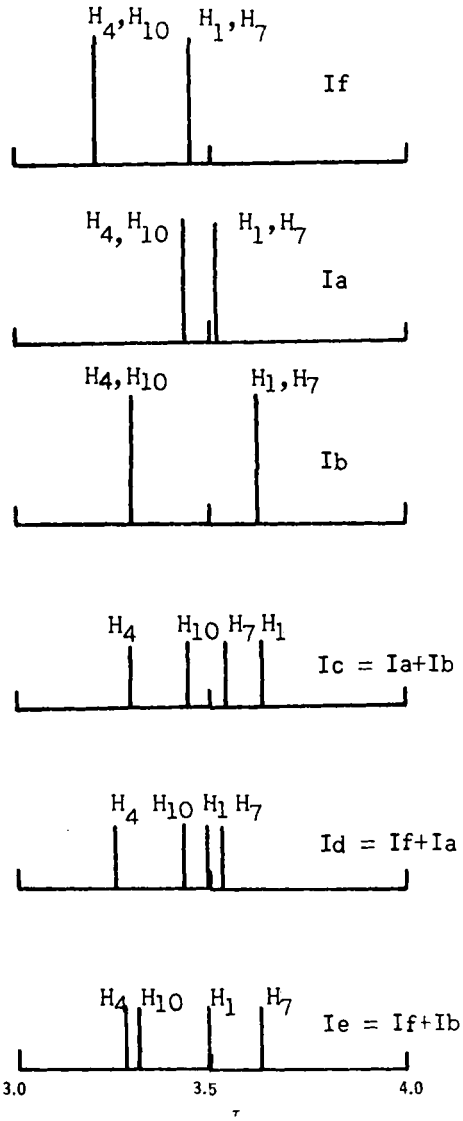
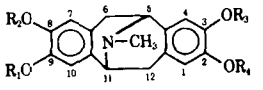


Figure 2—*Aromatic region of* Ia–Ie *showing the additivity of spectra.*

[3] Melting points were taken with a Thomas-Hoover melting-point apparatus. UV spectra were measured in ethanolic solutions with a Cary model 14 spectrophotometer. IR spectra were determined with a Perkin-Elmer 237B grating IR spectrophotometer. NMR spectra were taken in suitable solvents, using tetramethylsilane as an internal standard, with a Varian Associates model A-60D NMR spectrometer and are recorded for all new compounds in Table I. Mass spectra were determined by a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

Table III—NMR Data[a] for I*a*–I*g*



I*a*: $R_1 = R_3 = H, R_2 = R_4 = CH_3$
I*b*: $R_1 = R_3 = CH_3, R_2 = R_4 = H$
I*c*: $R_1 = R_4 = H, R_2 = R_3 = CH_3$
I*d*: $R_1 = H, R_2 = R_3 = R_4 = CH_3$
I*e*: $R_2 = H, R_1 = R_3 = R_4 = CH_3$
I*f*: $R_1 = R_2 = R_3 = R_4 = CH_3$
I*g*: $R_1 = R_2 = R_3 = R_4 = H$

	H_1	H_4	H_7	H_{10}	OCH_3 C_2	OCH_3 C_3	OCH_3 C_8	OCH_3 C_9	$N-CH_3$
I*a*	3.52	3.43	3.52	3.43	6.33	—	6.33	—	7.64
I*b*	3.62	3.30	3.62	3.30	—	6.23	—	6.23	7.63
I*c*	3.63	3.29	3.52	3.44	—	6.27	6.34	—	7.65
I*d*	3.49	3.25	3.52	3.43	6.35	6.28	6.35	—	7.65
I*e*	3.49	3.29	3.64	3.30[b]					
I*f*	3.46	3.22	3.46	3.22	6.32	6.23	6.32	6.23	7.64
I*g*	3.71	3.51	3.71	3.51	—	—	—	—	7.67

[a] All spectra were taken in dimethyl sulfoxide-d_6 and recorded in τ. [b] Values for Compound I*e* were taken from *Reference 13*; values for OCH_3 and $N-CH_3$ signals are not presently available.

and 30 ml. of phosphorus oxychloride was refluxed in 200 ml. of toluene for 1.5 hr. The reaction mixture was evaporated under vacuum to afford a brown oily residue. This residue was dissolved in 200 ml. of chloroform and shaken with 100 ml. of 10% NaOH. The chloroform layer was separated, washed with distilled water, dried (anhydrous K_2CO_3), and evaporated to give a reddish-brown oil. This oil crystallized from benzene to give 6.20 g. (57%) of VI*a*. Recrystallization from the same solvent yielded fine white needles, m.p. 177–178.5°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 240 (4.93), 270 (3.94, shoulder), 280 (3.96), 314 (3.75), and 328 (3.70).

Anal.—Calc. for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.33; H, 6.25; N, 2.66.

1-(3′-Benzyloxy-4′-methoxybenzyl)-6-benzyloxy-7-methoxyisoquinoline (VI*b*)—Compound V*b* (19.90 g., 0.0368 mole) was treated with 50 ml. of phosphorus oxychloride and worked up as already described to give VI*b* in 37% yield. An analytical sample was prepared by preparative TLC (silica gel F_{254}, Brinkmann, 2 mm.) using 5% methanol in chloroform as developing solvent. The zone was visualized under a UV lamp and eluted from the scraped band with methanol. The sample was crystallized from benzene as white needles, m.p. 146–147.5°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 240 (4.71), 270 (3.79, shoulder), 281 (3.84), 315 (3.54), and 328 (3.60).

Anal.—Calc. for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.30; H, 6.04; N, 2.67.

Table IV—Effect of Hydroxyl Group on *o*- and *m*-Protons[a]

	o-Protons	*m*-Protons
I*a*–I*f*	0.21	0.06
I*b*–I*f*	0.16	0.08
I*c*–I*f*	0.17	0.07
	0.22	0.06
I*d*–I*f*	0.21	0.06
I*e*–I*f*	0.18	0.08
Range	0.16–0.21	0.06–0.08
Average	0.19	0.07
Expected $o + m = 0.19 + 0.07 = 0.26$		
Observed I*g*–I*f* = 0.25 and 0.29		

[a] Upfield shifts in parts per million with respect to the I*f* aromatic protons.

1-(4′-Benzyloxy-3′-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxyisoquinolinium Iodide (VII*a*)—A mixture of 5 g. (0.0102 mole) of VI*a* and 50 ml. of methyl iodide in 30 ml. of dimethylformamide was refluxed for 1.5 hr. This was followed by another addition of 50 ml. of methyl iodide and continued reflux for 1.5 hr. Excess of methyl iodide was removed under vacuum to afford a brown liquid, which was diluted with anhydrous ether to precipitate a yellow solid. This solid was collected and washed thoroughly with anhydrous ether. Recrystallization from acetone yielded 4.0 g. (62%) of VII*a* as yellow prisms, m.p. 174.5–176°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 259 (4.55), 283 (3.62, shoulder), and 318 (3.78).

Anal.—Calc. for $C_{33}H_{32}INO_4$: C, 62.56; H, 5.09; N, 2.21. Found: C, 62.47; H, 4.92; N, 2.08.

1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-6-benzyloxy-7-methoxyisoquinolinium Iodide (VII*b*)—The isoquinoline VI*b* (3.70 g., 0.00753 mole) was treated with methyl iodide in dimethylformamide as already described to yield 82% of VII*b*. An analytical sample was obtained by recrystallization from acetone–methanol as yellow needles, m.p. 234–236°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 259 (4.68), 283 (3.70, shoulder), and 318 (3.97).

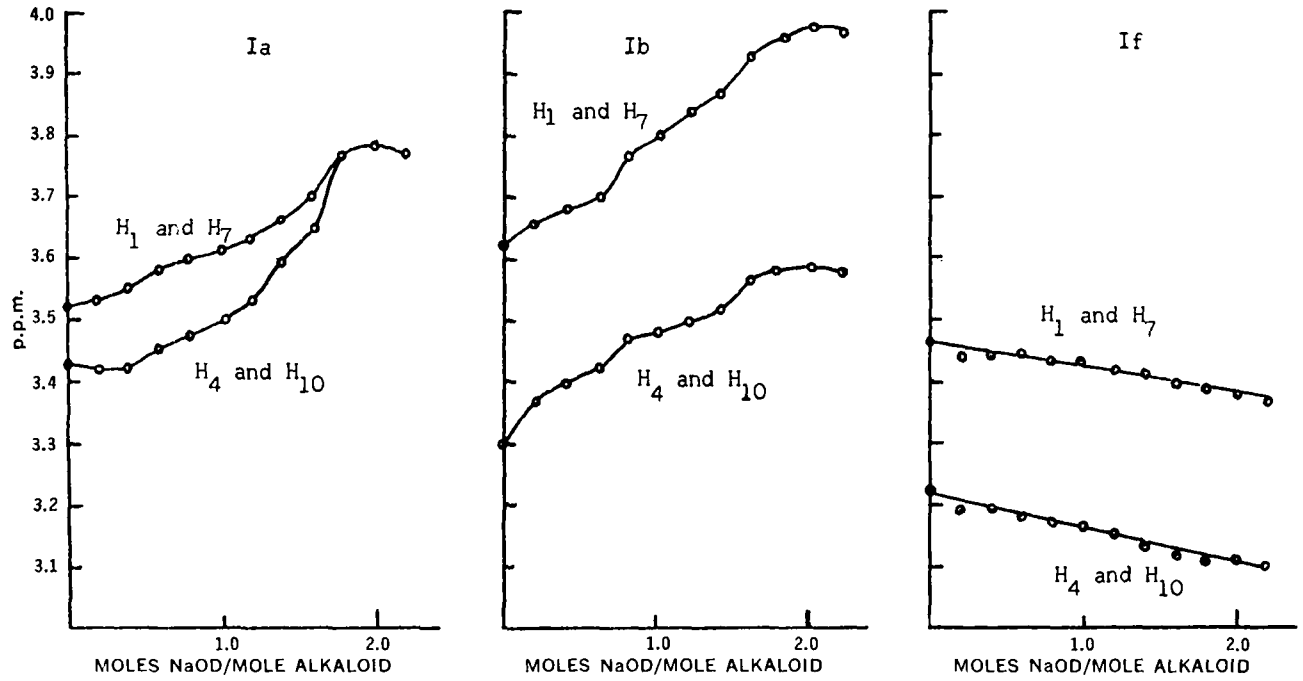


Figure 3—*Change in chemical shifts of aromatic protons on conversion into phenolate ions.*

Anal.—Calc. for $C_{33}H_{32}INO_4$: C, 62.56; H, 5.09; N, 2.21. Found: C, 62.36; H, 5.02; N, 2.00.

1 - (4′ - Benzyloxy - 3′ - methoxybenzyl) - 2 - methyl - 6 - methoxy-7 - benzyloxy - 1,2,3,4 - tetrahydroisoquinoline (VIII*a*)—Sodium borohydride (0.400 g.) was added portionwise to 0.208 g. (0.00328 mole) of *VIIa* in 40 ml. methanol and 0.5 ml. water. The resulting mixture was refluxed for 1 hr. After being cooled, methanol was removed under vacuum to give a white residue. Water (50 ml.) was added to this residue, and the resulting aqueous solution was extracted three times with ether. The combined ethereal solution was dried (anhydrous $MgSO_4$) and evaporated to yield a colorless residue. This residue was dissolved in petroleum ether (60–70°) and cooled to afford 0.099 g. (60%) of VIII*a* as white needles, m.p. 92–93° [lit. (8) m.p. 94–95°].

1 - (3′ - Benzyloxy - 4′ - methoxybenzyl) - 2 - methyl - 6 - benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (VIII*b*)—The methiodide VII*b* (0.211 g., 0.000333 mole) was reduced by sodium borohydride in aqueous methanol as described for VIII*a*. After the usual workup, the pale oil obtained was crystallized from ethanol–water to give VIII*b* (50%) as colorless needles, m.p. 95–97° [lit. (8, 9) m.p. 93.5–94.5° and 96–97°, respectively].

1 - (4′ - Benzyloxy - 3′ - methoxybenzyl) - 2 - methyl - 6 - methoxy-7-benzyloxy-1,2-dihydroisoquinoline (IX*a*)—To a suspension of 1.00 g. sodium borohydride in 40 ml. pyridine was added, portionwise, 3.63 g. (0.0057 mole) of VII*a*. The mixture was shaken occasionally until complete solution was effected. A second batch of 0.800 g. of sodium borohydride was then added to the solution, and shaking continued for 5 min. Ether was then added to the reaction mixture, followed by addition of water to decompose the resulting complex and excess sodium borohydride. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ethereal extract was dried (anhydrous K_2CO_3), and the solvent was removed by evaporation. Most of the pyridine remaining was removed under reduced pressure. The greenish-yellow oil obtained was dissolved in a few milliliters of absolute ethanol and cooled to afford 2.44 g. (84%) of IX*a* as white needles, m.p. 115–118°. An analytical sample was prepared by two recrystallizations from the same solvent, m.p. 115–118°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 255 (4.05, shoulder), 284 (3.78), and 337 (4.07).

Anal.—Calc. for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 78.22; H, 6.46; N, 2.84.

1 - (3′ - Benzyloxy - 4′ - methoxybenzyl) - 2 - methyl - 6 - benzyloxy-7-methoxy-1,2-dihydroisoquinoline (IX*b*)—Compound VII*b* (3.00 g., 0.00471 mole) was reduced with sodium borohydride in pyridine in the same manner as described for VII*a*. The greenish oil obtained was crystallized from absolute ethanol to give IX*b* in 81% yield. Three recrystallizations from the same solvent gave fine white needles, m.p. 123–126°; UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 254 (4.14, shoulder), 284 (3.63), and 333 (3.94).

Anal.—Calc. for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 77.80; H, 6.39; N, 2.74.

3,9-Dihydroxy-2,8-dimethoxy-*N*-methylpavinane (I*a*)—A mixture of 2.12 g. (0.0042 mole) of IX*a* in 4.2 ml. of phosphoric acid (85%) and 10.5 ml. of formic acid (97%) was heated at 120° for 4 hr. under an atmosphere of nitrogen. The reaction mixture was cooled, diluted with 50 ml. of water, and extracted twice with 30 ml. of chloroform. The aqueous layer was separated and basified with 20% ammonium hydroxide solution. The resulting solution was then extracted with chloroform (6 × 50 ml.). The combined chloroform extract was dried (anhydrous $MgSO_4$) and evaporated under vacuum to give a brown residue (about 1.2 g.). This residue was dissolved in a few milliliters of benzene–methanol (10:1), and colorless prisms were obtained under standing at room temperature. The crystals were filtered and washed with fresh solvent and ether, respectively, to give a white powder (0.35 g.). TLC analysis [silica gel, Eastman 6060, using benzene–methanol (3:2) as solvent] indicated that this residue contained one major component at R_f 0.39 and two minor ones at R_f 0.46 and 0.52. The mixture was then recrystallized twice from methanol to give 0.170 g. (12.3%) of I*a* as fine colorless needles, m.p. 250–251.5°, R_f 0.39; IR $\nu_{max.}^{KBr}$ cm.$^{-1}$: 3481 (phenolic OH) and 1605 (C=C); UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 226 (4.10, shoulder), 285 (3.88), 289 (3.89), and 293 (3.85, shoulder). High-resolution mass spectra—M^+ calc. for $C_{19}H_{21}NO_4$: 327.14705. Found: 327.146_7.

2,8-Dihydroxy-3,9-dimethoxy-*N*-methylpavinane (I*b*)—A mixture of 1.833 g. (0.00371 mole) of IX*b* in 3.8 ml. of phosphoric acid (85.6%) and 9.5 ml. of formic acid (97%) was heated under the same conditions as described for IX*a*. A similar workup procedure gave a brown residue (about 1.5 g.) from the basified reaction mixture. Silica gel TLC [benzene–methanol (3:2)] indicated a major component at R_f 0.55. This mixture was further fractionated by chromatography over a silica gel column (70 g., Baker 3405, 60–200 mesh) and eluted with a benzene–methanol (10:1) solvent. Fractions of 25 ml. were collected and analyzed by TLC. Fractions 22–35 were found to contain spots with R_f 0.55. All of these fractions were combined and evaporated to give a yellow residue. This residue was recrystallized from methanol–ether with cooling to afford 0.057 g. of I*b* as yellow needles, m.p. 205–207°. From the mother liquor, another 0.056 g. of I*b* was obtained by preparative TLC on a silica gel plate (Brinkmann F_{254}, 2 mm.) using chloroform–ethyl acetate–methanol (2:2:1) as the developing solvent. Compound I*b* appeared as a yellow zone under UV light. The yield of I*b* (0.113 g.) calculated from IX*b* was 9%; IR $\nu_{max.}^{KBr}$ cm.$^{-1}$: 3480 (phenolic OH) and 1601 (C=C); UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 226 (3.75, shoulder), 285 (3.51, shoulder), 289 (3.53), and 294 (3.49, shoulder). High-resolution mass spectra—M^+ calc. for $C_{19}H_{21}NO_4$: 327.14705. Found: 327.147_6.

2,3,8,9-Tetrahydroxy-*N*-methylpavinane (I*g*)—Compound I*f*, 0.510 g. (0.00153 mole), and 3 g. of anhydrous aluminum chloride were mixed in 5 ml. of anhydrous xylene and heated at 140–150° for 20 min., the temperature then being raised to 180° for 5 min. The dark-brown solution was allowed to cool, and then ice and concentrated hydrochloric acid were added to decompose the complex. A pale-green crystalline precipitate formed. This precipitate was filtered and recrystallized from 10% hydrochloric acid to give 0.324 g. of I*g* hydrochloride (64%) as white hexahedra, m.p. 213–216° [lit. (15) m.p. 209–213°].

The IR spectrum was identical with that of an authentic sample previously prepared in these laboratories (15), and a mixed melting-point determination showed no depression.

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