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Total Synthesis of (±)-Bisnorargemonine

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Abstract □ (±)-Bisnorargemonine (I) was synthesized by two alternate but similar routes, differing only in the relative positions of the methoxy and benzyloxy groups on the aromatic rings of the 1-benzylisoquinoline-derived moieties. Both the standard Bischler–Napieralski procedure and the Pictet–Gams modification were employed in the construction of the needed isoquinoline intermediates. Conversion of the latter to the methiodide followed by partial reduction to the *N*-methyl-1,2-dihydro form and, finally, acid-catalyzed cyclization provided (±)-I, which was identical with natural (−)-I except for melting point and optical rotatory power.

Keyphrases □ (±)-Bisnorargemonine—synthesis, structure identification □ Alkaloids, from benzylisoquinolines—synthesis, structure identification, (±)-bisnorargemonine □ UV spectrophotometry—structure, identification, (±)-bisnorargemonine □ NMR spectroscopy—structure, identification, (±)-bisnorargemonine

Bisnorargemonine, an alkaloid, was first isolated by Kier and Soine (1) from *Argemone munita* subsp. *rotundata* (Rydb) G. B. Ownb. It was shown to have a pavine-type ring system by diazomethylation to argemonine (II) (2) which had earlier been established (3, 4) as the (−)-rotatory form of known (±)-*N*-methylpavine (5). Furthermore, based on its unique NMR spectrum, Structure I had been postulated for natural bisnorargemonine (6).

The purposes of this study were to substantiate the suggested structure by an unequivocal synthesis and to provide a practical synthetic method for preparing the alkaloid for other related studies.

The successful synthesis of (±)-norargemonine (III) by Lee and Soine (7) provided a model procedure which could, presumably, be followed in the synthesis of (±)-I reported here. Scheme I[1] shows that the final step in the synthesis of III is by way of the acid-catalyzed ring closure of IV*c* through a C_4-protonated immonium intermediate (5) to provide the pavine-type skeleton. It is apparent that, following the same scheme, two alternate routes lead to the same racemic target compound, *i.e.*, IV*a* → I*a* and IV*b* → I*b*, I*a* and I*b* being identical. The first route, IV*a* → (±)-I, has a methoxyl group directing cyclization and was the subject of a previous communication (8). The alternate route, IV*b* → (±)-I, with a benzyloxy group directing cyclization, also was achieved but, considering the strong acid medium used in cyclization, it is very likely that ether cleavage occurred prior to cyclization and that the ensuing phenolic hydroxyl group was the actual directing group. Since the original communication (8) was of necessity brief, both synthetic schemes are described in detail here.

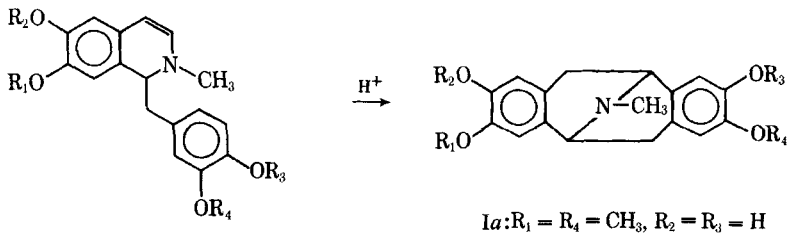
[1] Ph = phenyl in this and subsequent schemes.

DISCUSSION

The construction of the isoquinolines, XI*a* and XI*b*, was the key in the synthetic scheme to the target compound, (±)-I (Scheme II). One common way of achieving this objective has been catalytic dehydrogenation of the corresponding 1,2,3,4-tetrahydroisoquinolines as employed in the synthesis of III (7). Unfortunately, dehydrogenation was always accompanied by cleavage of the benzyloxy groups, and subsequent benzylation was necessary to resynthesize the benzyl ether. Exploration of the Pictet–Gams modification of the Bischler–Napieralski procedure (9) for the synthesis of XI*a* and XI*b* provided a more convenient route since the dehydrogenation step was eliminated.

As outlined in Scheme II, the β-methoxy-β-phenylethylamines (VII*a* and VII*b*) were prepared from the corresponding β-nitrostyrenes (V*a* and V*b*) by addition of sodium methoxide and subsequent reduction of the adducts (VI*a* and VI*b*) with lithium aluminum hydride, as described by Rosenmund *et al.* (10). The acids (VIII*a* and VIII*b*) were synthesized from *O*-benzylvanillin and *O*-benzylisovanillin according to the procedures of Douglas and Gulland (11) and Robinson and Sugasawa (12), respectively. Prior to condensation with the amines, VIII*a* and VIII*b* were converted to their acid chloride forms, IX*a* and IX*b*.

The amides, X*a* and X*b*, were readily obtained by interaction of VII*a* with IX*a* and of VII*b* with IX*b*, respectively. Compounds X*a* and X*b* were subsequently cyclized in one step with phosphorus oxychloride to XI*a* and XI*b*, respectively. The NMR spectral

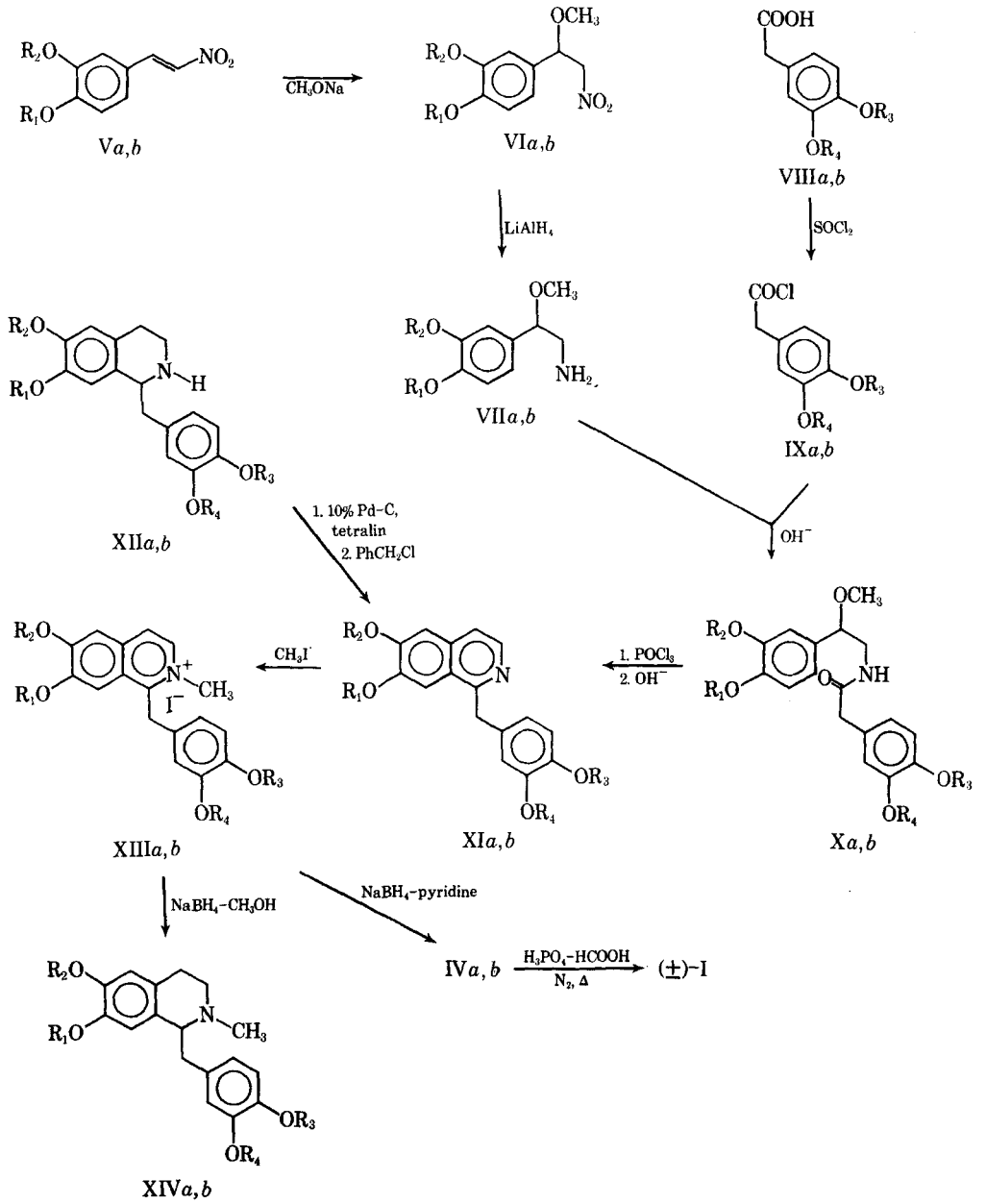


IV*a*: $R_1 = R_4 = CH_3$, $R_2 = R_3 = CH_2Ph$
IV*b*: $R_1 = R_4 = CH_2Ph$, $R_2 = R_3 = CH_3$
IV*c*: $R_1 = CH_2Ph$, $R_2 = R_3 = R_4 = CH_3$

I*a*: $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$
I*b*: $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
III: $R_1 = H$, $R_2 = R_3 = R_4 = CH_3$
II: $R_1 = R_2 = R_3 = R_4 = CH_3$

Scheme I

data for X*a* and X*b* as well as XI*a* and XI*b* are recorded in Table I. The loss of the β-OCH_3 singlets in the isoquinolines is clearly evident, and the singlet for the methylene group in the phenylacetyl moiety shifted downfield by about 1 p.p.m. when deshielded by attachment to the isoquinoline ring at the 1-position. The UV spectra for XI*a* and XI*b* (see *Experimental*) were also in keeping with those expected for 1-benzylisoquinoline chromophores (7). Compounds XI*a* and XI*b* could also be obtained, as previously mentioned, by catalytic dehydrogenation of the tetrahydroisoquinolines, XII*a* and XII*b*, synthesized according to Tomita and Kunitomo (13, 14). The products of dehydrogenation were a mixture of phenolic isoquinolines, which were not purified but were



Scheme II—For each compound shown: a, $R_1 = R_4 = CH_3$, $R_2 = R_3 = CH_2Ph$; *and* b, $R_1 = R_4 = CH_2Ph$, $R_2 = R_3 = CH_3$

Table I[a]—NMR Data for X*a*, X*b*, XI*a*, XI*b*, XIII*a*, XIII*b*, IV*a*, and IV*b*

	OCH_3	OCH_2Ph	$-\overset{O}{\overset{\|}{C}}-CH_2$	$\beta-OCH_3$
X*a*	6.17 (s, 6H)	4.89 (s, 4H)	6.57	6.93
X*b*	6.13 (s, 6H)	4.86 (s, 4H)	6.55	6.82

	OCH_3[b]				OCH_2Ph[b]				C_1-CH_2	C_3-H
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'		
XI*a*	—	6.16	6.25	—	4.81	—	—	4.96	5.49	1.71 (d, J = 5.8 Hz.)
XI*b*	6.00	—	—	6.18	—	4.87	4.98	—	5.57	1.63 (d, J = 5.7 Hz.)

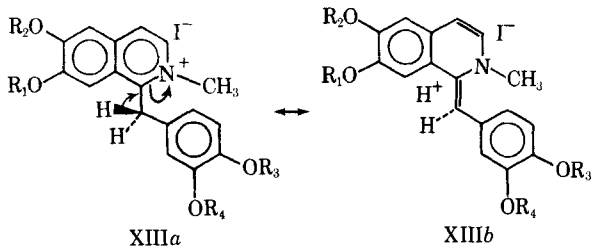
	OCH_3				OCH_2Ph				C_1-CH_2	$\overset{+}{N}-CH_3$	C_3-H and C_4-H *AB* quartet
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'			
XIII*a*	—	6.05	6.18	—	4.62	—	—	4.97	4.96[c]	5.55	1.39, 1.81 (J = 7 Hz.)
XIII*b*	5.85	—	—	6.18	—	4.72	4.97	—	5.05	5.65[d]	1.34, 1.69 (J = 6.8 Hz.)

	OCH_3[e]				OCH_2Ph[e]				C_1-H	$N-CH_3$	C_3-H (d of d) and C_4-H (d)	C_8-H
	C_6	C_7	C_3'	C_4'	C_6	C_7	C_3'	C_4'				
IV*a*	—	6.40	6.27	—	4.81	—	—	4.81	5.50 (t)	7.19 (s)	3.86, 4.55 ($J_{3,4}$ = 7.3 Hz.; $J_{1,3}$ = 1.2 Hz.)	3.72 (s)
IV*b*	6.24	—	—	6.24	—	5.06	4.91	—	5.52 (t)	7.25 (s)	3.89, 4.56 ($J_{3,4}$ = 7 Hz.; $J_{1,3}$ = 1.5 Hz.)	3.64 (s)

[a] For X*a*, X*b*, XI*a*, XI*b*, XIII*a*, and XIII*b*, τ values in $CDCl_3$ are given, while τ values in pyridine-d_5 are listed for IV*a* and IV*b*. [b] These assignments were made by comparison with model compounds reported by Brochmann-Hanssen and Hirai (18). [c] An approximate value; signal obscured by $C_4'-OCH_2Ph$. [d] This signal disappeared by making a deuterated methiodide salt (see *Experimental*). [e] These assignments were based on the observation by Barton *et al.* (15) that a substitution at the C_7-position is shielded due to the benzyl group at the C_1-position.

rebenzylated to afford XI*a* and XI*b*. Some loss of product is unavoidable due to simultaneous quaternization. The isoquinolines, XI*a* and XI*b*, were identical by both synthetic routes. Compounds XII*a* and XII*b* were converted to their hydrochlorides and were found to agree with the reported melting-point values (13, 14). This independent route used for the synthesis of XI*a* and XI*b* also served to confirm the previously assigned structures from the cyclization of amides X*a* and X*b*.

Conversion of XI*a* and XI*b* to the methiodides XIII*a* and XIII*b*, respectively, followed by sodium borohydride reduction in pyridine by the method of Barton *et al.* (15), provided the desired *N*-methyl-1,2-dihydroisoquinolines (IV*a* and IV*b*). The NMR data for XIII*a* and XIII*b* as well as for IV*a* and IV*b* are recorded in Table I. Characteristic N^+-CH_3 singlets for XIII*a* and XIII*b* were observed, but the most interesting effect of quaternization was on the $-CH_2$ protons attached to the 1-position. As compared to XI*a* and XI*b*, the signals for the C_1-CH_2 groups in XIII*a* and XIII*b* were shifted downfield by about 0.5 p.p.m. and appeared as broadened lines. This finding can be rationalized by the following resonance contribution causing electron withdrawal from the CH_2 protons to the isoquinoline ring system. Furthermore, this hyper-



XIII*a* XIII*b*

conjugative effect increases the bond order of C_1-CH_2, restricting free rotation around the bond. A further effect of quaternization is noted in the downfield shift of the signals for OCH_3 and OCH_2Ph at C_6 and C_7, whereas those at C_3' and C_4' are unaffected.

The structural assignments for XIII*a* and XIII*b* were confirmed further by reduction with sodium borohydride in aqueous methanol to give the *N*-methyl-1,2,3,4-tetrahydroisoquinolines, XIV*a* and XIV*b*, respectively, which corresponded in physical properties to the identical compounds reported by Kunitomo (16).

Compounds IV*a* and IV*b* showed characteristic UV absorptions for the 1,2-dihydroisoquinoline chromophore, and the structural assignments were further substantiated by the NMR spectra (Table I). The signals for $>N-CH_3$ were shifted upfield by more than 1.5 p.p.m. as compared to $\overset{+}{N}-CH_3$ in XIII*a* and XIII*b*. The C_3-H and C_4-H formed an *AB* quartet (J = 7 Hz.), with further splitting of the C_3-H by C_1-H (J = about 1.5 Hz.), which appeared as a broadened triplet around 5.5 p.p.m., indicating the long-range coupling between C_1-H and C_3-H as shown by Barton *et al.* (15).

The final step in the synthesis, acid-catalyzed cyclization of IV*a* → (±)-I and IV*b* → (±)-I, was carried out as described by Battersby and Binks (5), except care was taken to perform it under a nitrogen atmosphere. The reaction mixture was analyzed by combined TLC and column chromatography (CC), using natural I as the reference compound. The purified (±)-I's from both routes were identical to one another in their TLC, UV, IR, NMR, GLC, and mass spectral (MS) properties. They were also identical to natural I, except that (±)-I obtained from IV*a* showed a line-broadening effect in its NMR spectrum (dimethyl sulfoxide-d_6) taken at a 40° temperature in a microcell. Raising the probe temperature to 60 and 70° progressively sharpened the lines, and the resulting spectra were then virtually identical with those of natural I taken at 40° in a conventional NMR tube. The most likely explanation for the line broadening observed is a decreased resolution in the microcell, which was improved at higher temperatures since such line broadening was much less evident with the product obtained from IV*b* when measured in the usual NMR tube.

The yield of (±)-I from IV*a* was 1.5% of theory, whereas that from IV*b* was 21% of theory, suggesting that, at least in this case, the phenolic group is more favored as a directing group for the cyclization.

EXPERIMENTAL[2]

1-Methoxy-1-(3-benzyloxy-4-methoxyphenyl)-2-nitroethane (VI*a*)—3-Benzyloxy-4-methoxy-β-nitrostyrene (V*a*) was prepared by condensation of *O*-benzylisovanillin with nitromethane according to the method reported by Gairaud and Lappin (17). Addition of sodium methoxide to V*a* by the method of Rosenmund *et al.* (10) gave VI*a* in 65% yield, a pale-yellow powder from ether, m.p. 100–102°. IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 1551 and 1376 (strong, NO_2). NMR (τ, in $CDCl_3$): 6.82 (s, 3H, β-OCH_3), 6.11 (s, 3H, C_4-OCH_3), and 4.83 (s, 2H, C_3-OCH_2Ph).

[2] Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. UV spectra were taken in ethanol solutions with a Cary model 14 spectrophotometer. IR spectra were determined in mineral oil or KBr with a Perkin-Elmer 237B grating IR spectrophotometer. NMR spectra were measured with a Varian Associates model A-60D nuclear magnetic resonance spectrometer, using tetramethylsilane as an internal standard, and are recorded in Table I or in the following descriptions. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6D mass spectrometer. GLC was performed on a Perkin-Elmer 900 instrument equipped with dual flame-ionization detectors. Elemental analyses were performed by the Microanalytical Laboratory, School of Chemistry, University of Minnesota, and by M-H-W Laboratories, Garden City, Mich.

Anal.—Calc. for $C_{17}H_{19}NO_5$: C, 64.35; H, 6.03; N, 4.41. Found: C, 64.35; H, 5.80; N, 4.17.

1-Methoxy-1-(4-benzyloxy-3-methoxyphenyl)-2-nitroethane (VI*b*)—4-Benzyloxy-3-methoxy-β-nitrostyrene (V*b*), prepared from *O*-benzylvanillin and nitromethane, was reacted with sodium methoxide as described previously to afford VI*b* in 86% yield, a pale-yellow powder from methanol, m.p. 102–103.5°. IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 1540 and 1374 (strong, NO_2). NMR (τ, in $CDCl_3$): 6.73 (s, 3H, β-OCH_3), 6.09 (s, 3H, C_3-OCH_3), and 4.83 (s, 2H, C_4-OCH_2Ph).

Anal.—Calc. for $C_{17}H_{19}NO_5$: C, 64.35; H, 6.03; N, 4.41. Found: C, 64.50; H, 5.89; N, 4.25.

β-Methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (VII*a*)—To an ice-cooled and stirred suspension of 1.52 g. (0.040 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether was added dropwise a solution of 3.17 g. (0.010 mole) of VI*a* in 60 ml. of anhydrous tetrahydrofuran. This reaction mixture was refluxed for 3 hr. After being cooled, the resulting complex was decomposed by successive addition of wet ether, water, and a saturated solution of potassium sodium tartrate. The gel which formed was removed by filtration and washed with ether. The ether layer was separated from the filtrate, and the aqueous layer was extracted twice with fresh ether. The combined ethereal solution was washed with water, dried (anhydrous $MgSO_4$), and evaporated under vacuum to yield a pale-brown oil (VII*a*). IR $\nu_{max.}^{L.f.}$ cm.$^{-1}$: 3361 (NH_2). NMR (τ in $CDCl_3$): 8.59 (s, 2H, NH_2), 6.77 (s, 3H, β-OCH_3), 6.09 (s, 3H, C_4-OCH_3), and 4.78 (s, 2H, C_3-OCH_2Ph). Compound VII*a* was converted to the oxalate salt by mixing it in an ethereal solution with a calculated equivalent amount of oxalic acid in methanol. The white precipitate (3.29 g., 99% of theory) was collected and crystallized from methanol as feathers, m.p. 157–161°.

Anal.—Calc. for $C_{36}H_{44}N_2O_{10}$: C, 65.05; H, 6.67; N, 4.21. Found: C, 64.86; H, 6.87; N, 4.26.

β-Methoxy-β-(4-benzyloxy-3-methoxyphenyl)ethylamine (VII*b*)—Lithium aluminum hydride reduction of VI*b* was carried out as described previously to give VII*b* as a pale-brown oil in virtually quantitative yield. IR $\nu_{max.}^{L.f.}$ cm.$^{-1}$: 3361 (NH_2). NMR (τ in $CDCl_3$): 8.12 (s, 2H, NH_2), 6.73 (s, 3H, β-OCH_3), 6.10 (s, 3H, C_3-OCH_3), and 4.85 (s, 2H, C_4-OCH_2Ph). The oxalate salt of VII*b*, prepared as described previously for VII*a*, provided featherlike white crystals from methanol, m.p. 179–184°.

Anal.—Calc. for $C_{36}H_{44}N_2O_{10}$: C, 65.05; H, 6.67; N, 4.21. Found: C, 65.15; H, 6.85; N, 4.02.

***N*-(4′-Benzyloxy-3′-methoxyphenylacetyl)-β-methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (X*a*)**—4-Benzyloxy-3-methoxyphenylacetic acid (VIII*a*) was prepared by the method of Douglas and Gulland (11). This acid (1.36 g., 0.005 mole) was refluxed with 2.5 ml. (0.035 mole) of thionyl chloride in 25 ml. of chloroform for 2 hr. The reaction mixture was evaporated, and the excess thionyl chloride was removed by repeated addition and evaporation of anhydrous toluene. The oily residue of acid chloride (IX*a*) was dissolved in 30 ml. of dry benzene; the resulting solution was added dropwise, with stirring and cooling, to a mixture of 30 ml. of 10% NaOH and 30 ml. benzene solution containing VII*a* (1.66 g., 0.005 mole of amine) prepared from its oxalate salt. After the addition, the reaction mixture was stirred for 1 hr. at 0°. The benzene layer was separated, and the aqueous layer was extracted twice with fresh benzene. The combined benzene extract was washed successively with 5% hydrochloric acid and water and dried over anhydrous potassium carbonate. Removal of benzene under vacuum gave a yellow oil, which was crystallized in ethanol to give 1.6 g. (59%) of X*a* as white fine needles, m.p. 96.5–98.5°. IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 3271 (associated >N—H) and 1643 (C=O).

Anal.—Calc. for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 73.43; H, 6.51; N, 2.44.

***N*-(3′-Benzyloxy-4′-methoxyphenylacetyl)-β-methoxy-β-(4-benzyloxy-3-methoxyphenyl)ethylamine (X*b*)**—3-Benzyloxy-4-methoxyphenylacetic acid (VIII*b*) was prepared according to the method described by Robinson and Sugasawa (12). This acid was converted into acid chloride (IX*b*) and then condensed with the amine (VII*b*) as described in the preparation of X*a*. The reaction product after workup was crystallized from ethanol to give X*b* (72%) as a white powder, m.p. 112–114°. IR $\nu_{max.}^{mineral\ oil}$ cm.$^{-1}$: 3333 (associated >N—H) and 1648 (C=O).

Anal.—Calc. for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 72.97; H, 6.60; N, 2.39.

1-(3′-Methoxy-4′-benzyloxybenzyl)-6-benzyloxy-7-methoxyisoquinoline (XI*a*)—*Method A: Cyclization of the Amide, X*a—A mixture of 0.37 g. (0.0007 mole) of X*a* and 0.9 ml. (0.01 mole) of phosphorus oxychloride in 6 ml. of toluene was refluxed for 1.5 hr. The reaction mixture was evaporated under vacuum to give a dark-brown oily residue. This residue was then taken up in chloroform and shaken with dilute ammonium hydroxide solution. The chloroform layer was separated, dried (anhydrous K_2CO_3), and evaporated under vacuum to yield a dark-brown oil. The oil was crystallized from benzene as a white residue and recrystallized from the same solvent to afford 0.13 g. (38%) of XI*a*, m.p. 146–147°. UV $\lambda_{max.}^{EtOH}$ nm. (log ε): 240 (5.37), 270 (4.10, shoulder), 280 (4.11), 315 (3.88), and 328 (3.92).

Anal.—Calc. for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 77.91; H, 5.97; N, 2.66.

*Method B: Dehydrogenation of 1,2,3,4-Tetrahydroisoquinoline, XII*a—Compound XII*a* was synthesized according to Tomita and Kunitomo (14). A mixture of 4.6 g. (0.0094 mole) of XII*a* and 1 g. of 10% palladium-on-charcoal in 50 ml. of tetralin was stirred and heated under an atmosphere of nitrogen for 1.5 hr. This was followed by another addition of 1 g. of catalyst and heating for another 30 min. The reaction mixture was filtered immediately to remove the catalyst; the filtrate, after being cooled, was diluted with excess anhydrous ether to produce a yellow solid. The solid was collected by filtration and washed well with anhydrous ether, yield 1.8 g. TLC analysis (alumina, chloroform and 95% ethanol in 20:1 ratio) showed that the solid was a mixture of more than three components. This mixture (1.8 g.) was then mixed with 1.6 g. of benzyl chloride and 0.9 g. of anhydrous potassium carbonate in 30 ml. of anhydrous methanol and refluxed for 3 hr. The reaction mixture was filtered immediately to remove potassium carbonate. Removal of methanol under vacuum gave a dark-brown residue, which was further purified by passing it through a neutral alumina[3] (70 g.) column using chloroform as the eluting solvent. The first 150 ml. of eluant was evaporated to give an oil which crystallized from a benzene–ether mixture. This was recrystallized from benzene to yield 0.63 g. (14% from XII*a*) of XI*a*, m.p. 146–147°. The IR spectrum was identical with XI*a* prepared from X*a*.

1-(3′-Benzyloxy-4′-methoxybenzyl)-6-methoxy-7-benzyloxyisoquinoline (XI*b*)—*Method A: Cyclization of the Amide, X*b—Following the same procedure as in the synthesis of XI*a* from X*a*, the amide X*b* was cyclized by treating with phosphorus oxychloride in refluxing toluene to give XI*b* in 49% yield. The product was crystallized from benzene as fine white needles, m.p. 169–171°. UV $\lambda_{max.}^{EtOH}$ nm. (log ε): 240 (4.62), 270 (3.59, shoulder), 279 (3.59), 314 (3.29), and 328 (3.39).

Anal.—Calc. for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.21; H, 6.09; N, 2.83.

*Method B: Dehydrogenation of 1,2,3,4-Tetrahydroisoquinoline, XII*b—Compound XII*b* was prepared by the procedure described by Tomita and Kunitomo (13). By following the same procedure already described, XII*b* was dehydrogenated and subsequently benzylated to give XI*b* in 38% yield. The IR spectrum was identical with the sample prepared from X*b*.

1-(3′-Methoxy-4′-benzyloxybenzyl)-2-methyl-6-benzyloxy-7-methoxyisoquinoline Iodide (XIII*a*)—A solution of 0.10 g. of XI*a* in 2 ml. of dimethylformamide and 1 ml. methyl iodide was refluxed for 1.5 hr. This was followed by addition of 1 ml. of methyl iodide and continuous heating for another 30 min. After being cooled, the reaction mixture was evaporated; the resulting solution was diluted with enough anhydrous ether to cause complete crystallization. The crystals deposited were filtered off and washed well with anhydrous ether. Recrystallization from an acetone–methanol mixture gave 0.12 g. (91%) of XIII*a* as yellow needles, m.p. 174–176.5°. UV $\lambda_{max.}^{EtOH}$ nm. (log ε): 258 (4.74), 286 (4.03, shoulder), and 320 (4.18).

Anal.—Calc. for $C_{33}H_{32}INO_4$: C, 62.56; H, 5.09; N, 2.21. Found: C, 62.27; H, 5.03; N, 1.92.

1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-6-methyl-7-benzyloxyisoquinoline Iodide (XIII*b*)—By the same procedure already described, XIII*b* was prepared from XI*b*. The crude product was recrystallized from the methanol–acetone mixture to give fine yellow needles in almost quantitative yield, m.p. 200–202°. UV $\lambda_{max.}^{EtOH}$ nm. (log ε): 259 (4.84), 286 (3.82 shoulder), and 318 (4.04).

[3] Woelm, activity grade I.

Anal.—Calc. for $C_{33}H_{39}INO_4$: C, 62.56; H, 5.09; N, 2.21. Found: C, 62.43; H, 5.12; N, 2.20.

To assign the signal for the N^+—CH_3 group, iodomethane-d_3 was used to prepare XIII*b* in the *N*-methyl-d_3 form. The singlet at 5.56 τ (Table I) was missing from the spectrum of the deuterated species as compared with that of the undeuterated one[4].

1-(3′-Methoxy-4′-benzyloxybenzyl)-2-methyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (XIV*a*)—Sodium borohydride (0.40 g.) was added, portionwise, into a suspension of 0.203 g. (0.00032 mole) of XIII*a* in 40 ml. of methanol and 6 drops of water. Following the addition, the mixture was refluxed for 1 hr. The reaction mixture was evaporated, and the resulting residue was dissolved in water (50 ml.). The aqueous solution was extracted with ether (6 × 50 ml.); the combined ethereal extract was dried (anhydrous K_2CO_3) and evaporated under vacuum to give a pale-brown oil. This oil crystallized from 95% ethanol to give 0.136 g. of XIV*a* as fine colorless needles, m.p. 89–92° [lit. (16) m.p. 91–93°].

1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (XIV*b*)—The methiodide XIII*b* (0.11 g., 0.00017 mole) was reduced with sodium borohydride as described for XIII*a*. The oily product crystallized from 90% ethanol to give XIV*b* (96%) as fine colorless needles, m.p. 88.5–89.5° [lit. (16) m.p. 89.5–90.5°].

1-(3′-Methoxy-4′-benzyloxybenzyl)-2-methyl-6-benzyloxy-7-methoxy-1,2-dihydroisoquinoline (IV*a*)—The methiodide XIII*a* (0.100 g., 0.0016 mole) was added, portionwise, to a suspension of 0.025 g. of sodium borohydride in 4 ml. of pyridine. The mixture was shaken until the methiodide dissolved completely. Another 0.020 g. of sodium borohydride was then added, and the mixture was shaken for another 5 min. The reaction mixture was then taken up in ether and shaken with water (30 ml.); the aqueous layer was extracted twice with fresh ether. The combined ethereal extract was dried (anhydrous K_2CO_3), and evaporated to remove ether. Traces of pyridine remaining in the residue were removed by applying high vacuum at room temperature. The oily residue was then dissolved in a few milliliters of ethanol and cooled in a refrigerator to yield 0.046 g. (57%) of IV*a* as fine colorless needles. Recrystallization from the same solvent gave m.p. 64–67°. This compound decomposed slowly upon standing in the air. UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 255 (3.58, shoulder), 285 (3.25), and 334 (3.54).

Anal.—Calc. for $C_{34}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 78.32; H, 6.52; N, 2.50.

1-(3′-Benzyloxy-4′-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2-dihydroisoquinoline (IV*b*)—Sodium borohydride reduction of 0.300 g. (0.00048 mole) of the methiodide, XIII*b*, in the same manner as described for VI*a* gave an oily product which crystallized from methanol to yield IV*b* (57%). Recrystallization from ethanol gave colorless rosettes, m.p. 93–97°. UV $\lambda_{max.}^{EtOH}$ nm. (log ϵ): 256 (3.89, shoulder), 285 (3.58), and 336 (3.96).

Anal.—Calc. for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 78.16; H, 6.64; N, 2.66.

Cyclization of IV*a* to (±)-Bisnorargemonine (I)—A mixture of 1.50 g. (0.0030 mole) of IV*a* in 3 ml. of 85.6% phosphoric acid and 7.5 ml. of 90.8% formic acid was heated for 4 hr. at 120° under an atmosphere of nitrogen. The reaction mixture, after being cooled, was diluted with water and extracted twice with chloroform (2 × 50 ml.). The aqueous layer was then made alkaline with dilute ammonia (10%) and again extracted with chloroform (6 × 100 ml.). The combined chloroform extract was then dried (anhydrous K_2CO_3) and evaporated under vacuum to yield a brown residue (about 1 g.). TLC analysis on silica gel [benzene–methanol (3:2)] indicated more than three components in this mixture, one of which corresponded to natural I with R_f 0.50. This mixture was further fractionated by passing it through a silica gel column[5] (20 g., 60–200 mesh), with benzene–methanol (3:2) as the eluant. Fractions 10–20 (10 ml. per fraction) showed spots corresponding to R_f 0.50. All these fractions were combined and evaporated under vacuum to give a greenish-brown residue. This residue was then dissolved in a small amount of chloroform, and crystallization occurred upon standing at room temperature. The crystals collected were gelatinous but, on drying under vacuum at 100° for 24 hr., gave 0.015 g. (1.5% from IV*a*) of a white powder, m.p. 231.5–233.5°. The IR (KBr) and UV spectra were identical in every aspect with those of natural I. Attempts were made to analyze this synthetic material by GLC. A silyl derivative was prepared by mixing 1 mg. of the powder in 5 ml. anhydrous ether with 0.5 ml. of trimethylsilyl chloride, 0.5 ml. of hexamethyldisilazane, and a few drops of pyridine. The supernatant from the mixture was analyzed on an OV-1 column (3% on Chromosorb W, at 215° column temperature, with nitrogen as the carrier gas at 30 ml./min.) and gave a single peak with retention of 11.4 min. A silyl derivative of natural I was similarly prepared and gave, under the same conditions, an identical retention time.

The NMR spectrum (in dimethyl sulfoxide-d_6) of this synthetic material taken in a microcell at 40° showed line broadening. Raising the probe temperature to 60 and 70° improved the line shape, and the spectra obtained were identical with those of natural I taken in the same solvent.

Cyclization of IV*b* to (±)-Bisnorargemonine (I)—A mixture of 1.3 g. (0.0025 mole) of IV*b* in 2.6 ml. of 85.6% phosphoric acid and 6.5 ml. of 97% formic acid was heated, and the reaction mixture was worked up as described previously to afford a reddish-brown oil (about 1 g.). This oil was fractionated on a silica gel column (70 g.), with benzene–methanol (10:1) as the eluting solvent. Fractions 20–40 (20 ml. per fraction) were combined and evaporated to give a pale-brown residue. This residue was crystallized in chloroform to afford 0.18 g. (21% from VI*b*) of a white powder, m.p. 226–227°. The IR, MS, UV, and GLC behaviors were identical with those of natural I and synthetic (±)-I from the IV*a* route. The NMR spectrum taken at 40° in a normal cell showed a much less line-broadening effect and was virtually identical with the spectrum of natural I.

[4] This led to the discovery of an erroneous assignment in a previous paper by Lee and Soine (7). For Compound XV cited therein, the singlet at 5.54 τ should be assigned to the N^+—CH_3 group, while the singlet at 5.02 τ should be assigned to the C_1—CH_2 group.

[5] Baker Analyst No. 3405.

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