Biomimetic Syntheses of the Bisindole Alkaloids Villalstonine and Alstonisidine[1]

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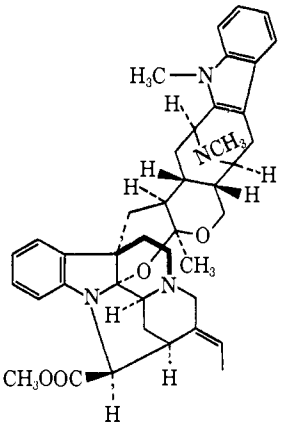
Abstract: Villalstonine (**1**) and alstonisidine (**25**) have been synthesized from macroline (**3**) and, respectively, pleiocarpamine (**2**) and quebrachidine (**8**). These syntheses are stereospecific and biomimetic, and represent the first syntheses of any kind in this group of bisindole alkaloids. In the case of alstonisidine, this synthesis, with investigations of model compounds, permits revision of the earlier proposed structure **7** to the isomeric **25**.

Villalstonine (**1**)[3,4] is the major alkaloid of *Alstonia muelleriana*,[5] *A. macrophylla*,[3,4,6] and *A. spectabilis*[6] (=*A. somersetensis*, =*A. villosa*).[7] Structure **1**, being a "bisindole," can be envisaged as arising biogenetically by reaction of two "monomeric" indole alkaloids. The elegant chemical work of Schmid and his coworkers[4] included the degradation of villalstonine to the known alkaloid pleiocarpamine (**2**) and the hitherto unknown base macroline (**3**). Macroline has not yet



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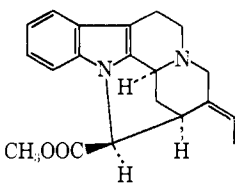

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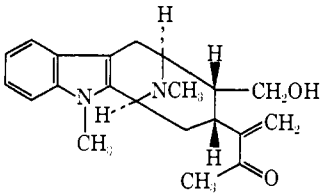

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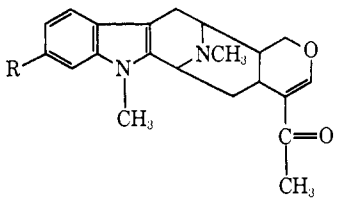
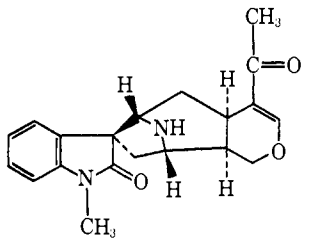
been found as such in nature, but it can clearly be regarded as a possible biogenetic precursor of the known "monomeric" *Alstonia* alkaloids alstonerine (**4**),[8] alstophylline (**5**)[9] (assuming the stereochemistry to be the same in **3**, **4** and **5**), and alstonisine (**6**).[5,10] Schmid[4]



4, R = H
5, R = OCH_3



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envisaged that electrophilic addition of the enone function of macroline (**3**) to the β position of the indole nucleus in pleiocarpamine (**2**), followed by ring closure reactions, could generate the novel contiguous acetal–aminoacetal functions of villalstonine.

Recently,[11] we proposed structure **7** for the bisindole alkaloid alstonisidine[5] on the basis of spectral and limited chemical investigations. This proposed structure (assuming normal stereochemistries) was regarded as arising from condensation of macroline (**3**) and quebrachidine (**8**),[12] although at that stage[11] the presence of a quebrachidine-like portion had been inferred almost entirely from mass spectra. A biogenesis for structure **7** was proposed,[11] involving first an electrophilic substitution by the macroline enone ortho to the indoline nitrogen of quebrachidine, and then ring closure reactions giving the aminoacetal function. More recently,[13] traces of quebrachidine (**8**) have been found in *A. muelleriana* bark, which strengthens the hypoth-

(1) Portions of this work have been published in preliminary form: (a) D. E. Burke and P. W. Le Quesne, *J. Chem. Soc., Chem. Commun.*, 678 (1972); (b) D. E. Burke, J. M. Cook, and P. W. Le Quesne, *ibid.*, 697 (1972). See also J. M. Cook, Ph.D. Thesis, University of Michigan, 1971; D. E. Burke, Ph.D. Thesis, University of Michigan, 1972.

(2) To whom inquiries should be addressed.

(3) C. E. Nordman and S. K. Kumra, *J. Amer. Chem. Soc.*, **87**, 2059 (1965).

(4) M. Hesse, H. Hürzeler, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, **48**, 689 (1965); M. Hesse, F. Bodmer, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *ibid.*, **49**, 1173 (1966).

(5) R. C. Elderfield and R. E. Gilman, *Phytochemistry*, **11**, 339 (1972).

(6) T. M. Sharp, *J. Chem. Soc.*, 1227 (1934).

(7) J. Monachino, *Pac. Sci.*, **3**, 133 (1949).

(8) J. M. Cook, P. W. Le Quesne, and R. C. Elderfield, *Chem. Commun.*, 1306 (1969).

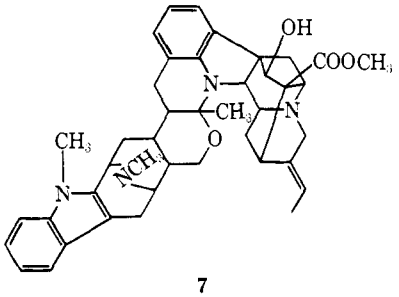
(9) T. Kishi, M. Hesse, C. W. Gemenden, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta*, **48**, 1349 (1965).

(10) C. E. Nordman and K. Nakatsu, *J. Amer. Chem. Soc.*, **85**, 353 (1963).

(11) J. M. Cook and P. W. Le Quesne, *J. Org. Chem.*, **36**, 582 (1971).

(12) M. Gorman, A, L. Burlingame, and K. Biemann, *Tetrahedron Lett.*, 39 (1963).

(13) D. E. Burke, G. A. Cook, J. M. Cook, K. G. Haller, H. A. Lazar, and P. W. Le Quesne, manuscript in preparation.



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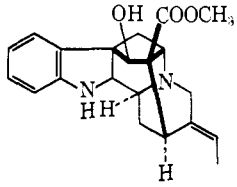

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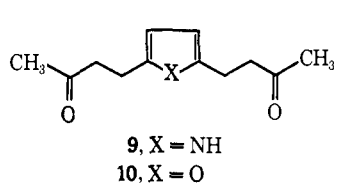
esis that this alkaloid could react with macroline or a "macroline equivalent" to generate alstonisidine.

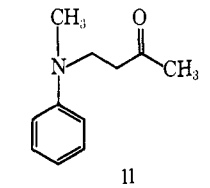
The likelihood that preformed monomeric indole alkaloids, or functionalized derivatives, react *in vivo* to give bisindole alkaloids is of much phytochemical significance. First, structural relationships between the two reacting units can be of potential taxonomic importance;[14] and secondly, it is important to determine whether the new structural and stereochemical features of the linkages between the halves of the bisindole arise from discrete reactions representing some unique biosynthetic capability of the plant species concerned. We have therefore investigated biomimetic reactions in this area, which culminate in simple syntheses of alstonisidine and villalstonine, and a revision of structure for the former.

Acid-catalyzed Michael and vinylogous Michael-type reactions offer mechanistically general approaches to the additions and substitutions to be considered. We searched the literature for ortho alkylation of an aniline by an enone as a model for our proposed biogenetic scheme.[11] Precedent for this reaction was lacking, although Webb and Borcherdt had prepared[15] 2,5-bis-(3-oxobutyl)pyrrole (**9**) and its furan analog **10** from methyl vinyl ketone and pyrrole and furan, respectively, in aqueous acid solution. We therefore performed the following model reactions. Methyl vinyl ketone and *N*-methylaniline under acidic conditions gave only 4-(*N*-methylanilino)-2-butanone (**11**). With a water–SO_2 mixture[15] only the unchanged aniline and the sulfone **12** were obtained. C-Alkylation was also not observed with *N*-methylacetanilide and methyl vinyl ketone (*cf.* ref 16 and 17). Similar results were obtained with indoline, no trace of the C-alkylated product **14**, which might have arisen from **13** as shown, being detected.

In 1 *N* aqueous hydrochloric acid at 20°, indoline and methyl vinyl ketone gave only the β-amino ketone **15** in 95% yield. The structure was established from spectra and from the ready retro-Michael conversion[18] by acetic anhydride and pyridine into *N*-acetylindoline.



9, X = NH
10, X = O



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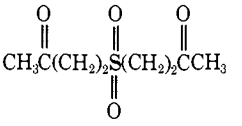

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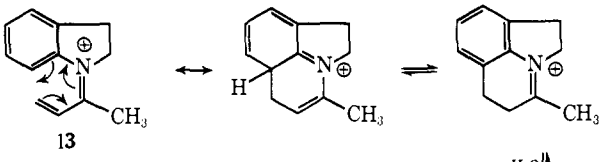

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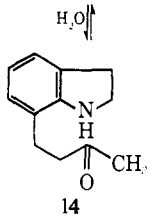

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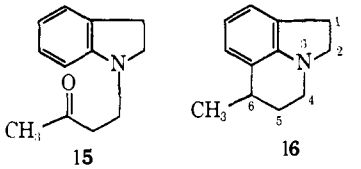

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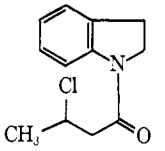

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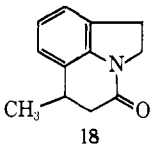

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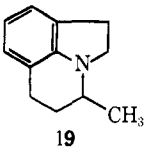

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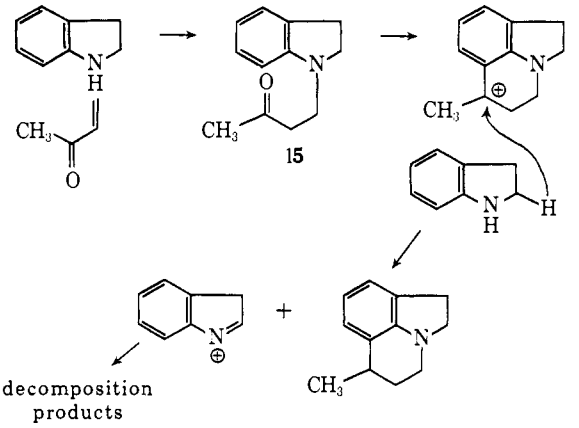
When the reaction was heated, only 10% of **15** was detected; instead, up to 21% of indoline was recovered, and a new compound, $C_{12}H_{15}N$, was obtained in up to 43% yield. That this compound was 6-methyllilolidine (**16**) was established by unambiguous synthesis. This, patterned after Hallas and Taylor,[19] began with condensation of 3-chlorobutyryl chloride with indoline to give the chloroamide **17**, which on heating with aluminum chloride gave the cyclized amide **18**. This compound with lithium aluminum hydride gave **16**, identical with that obtained from indoline and methyl vinyl ketone. We suggest that **16** could arise as in Scheme I, in which the hydride necessary for the reduction comes from indoline.

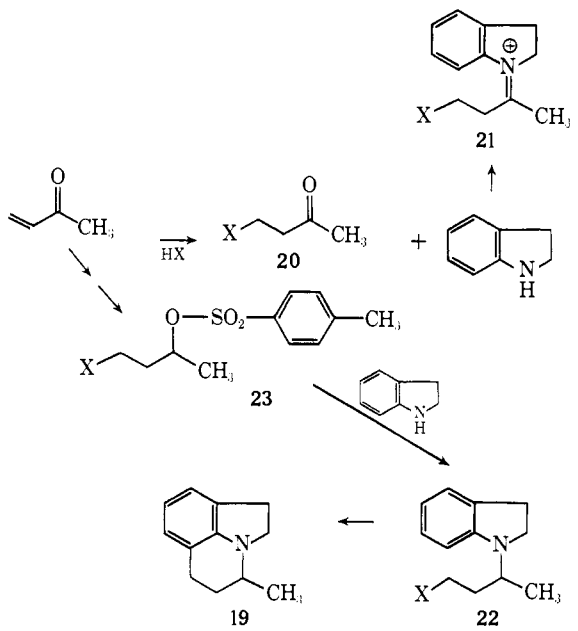
These *in vitro* reactions clearly pointed away from the biogenetic hypothesis outlined in our earlier paper.[11] However, since macroline (**3**) is known only as a degradation product, albeit appropriately funtionalized, and has not yet been detected in nature, we investigated some addition reactions of derivatives of methyl vinyl ketone with indoline in which the enone-derived carbon atoms could be made to add in the opposite sense, to give 4-methyllilolidine (**19**), the analog of **7**. We could then have prepared a suitably modified derivative of macroline if necessary. The general approach is shown in Scheme II.

(14) M. Hesse, I. Kompis, and H. Schmid, *Lloydia*, **34**, 269 (1971).
(15) I. D. Webb and G. T. Borcherdt, *J. Amer. Chem. Soc.*, 73, 752 (1951).
(16) M. Sacha and R. Patel, *J. Indian Chem. Soc.*, 33, 129 (1956).
(17) J. Colonge and M. Pichat, *Bull. Soc. Chim. Fr.*, 178 (1949).
(18) E. Bergmann, D. Ginsburg, and R. Pappo in "Organic Reactions," Vol. X, R. Adams, Ed., Wiley, New York, N. Y., 1959, p 187.
(19) G. Hallas and D. C. Taylor, *J. Chem. Soc.*, 1518 (1963).

Scheme I. Possible Route to 6-Methyllilolidine from Indoline and Methyl Vinyl Ketone



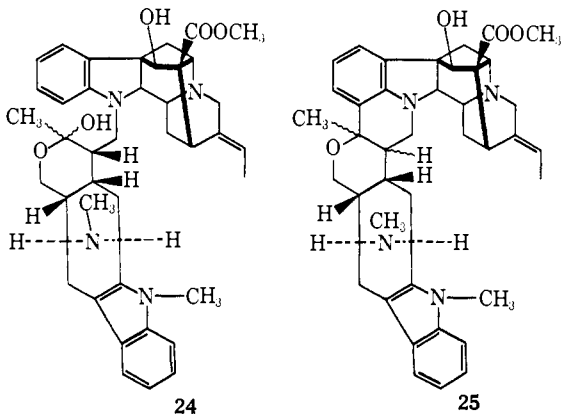
Scheme II. Synthesis of 4-Methyllilolidine from Indoline and Methyl Vinyl Ketone



Indoline perchlorate with methyl ethyl ketone[20] (**20**, X = H) gave the iminium perchlorate (**21**, X = H), which with sodium borohydride[21] gave *N-sec*-butylindoline (**22**, X = H) in 96% yield. 4-Acetoxy-2-butanone (**20**, X = CH_3COO), however, with indoline perchlorate gave, after reduction with sodium borohydride, 6-methyllilolidine (**16**). Clearly the indoline had displaced the acetate group from the 4-acetoxy-2-butanone, and the resulting ketone had cyclized as before. 4-Methoxy-2-butanone (**20**, X = OCH_3) was similarly unsuccessful, giving with indoline perchlorate after subsequent reduction indoline, 6-methyllilolidine (**16**), and also *N*-isopropylindoline, which arose from retro-aldol decomposition of the iminium ion (**21**, X = OCH_3) (*cf.* ref 20) and reduction of the resulting isopropylidene iminium salt. However, when 4-methoxy-2-tosyloxybutane (**23**, X = OCH_3) was allowed to react with indoline[22] and the indoline (**22**, X = OCH_3) treated with phosphorus pentoxide–phosphoric acid[23] at 200°, 4-methyllilolidine (**19**) was obtained in 30% yield. The structure is assigned from spectral data and by comparison with 6-methyllilolidine (**16**).[24]

This work clearly implies that if macroline is a true biogenetic precursor of alstonisidine, the reaction with quebrachidine is unlikely to take place in the manner suggested in our earlier proposal,[11] but it does allow for a suitably functionalized macroline derivative to give with quebrachidine an alkaloid of structure **7**.

We therefore turned first to macroline (**3**) itself, preparing it from villalstonine (**1**) using the reactions described by Schmid and his coworkers,[4] with some modifications. Macroline (**3**) was treated with quebrachidine (**8**) in 0.2 *N* aqueous hydrochloric acid at 20°. During 72 hr, a new product accumulated, as judged by tlc. No other compounds than the starting materials were observed. The new compound, isolated by preparative layer chromatography, was labile, reverting to starting materials on treatment with more concentrated acid, on warming, and slowly during chromatography. Its molecular weight was 690 (mass spectrometry), and the infrared spectrum showed only one carbonyl peak, that at 1735 cm^{-1} from quebrachidine. These data for the compound, in particular the ready reversibility of its

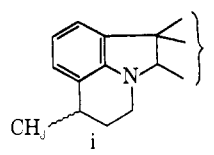


formation, are in complete accord with the work on model compounds described above, and clearly indicate the structure **24**. The absence of any ketonic infrared peak strongly suggests that, as expected once Michael addition has taken place, the now unconjugated ketone group from macroline forms a hemiacetal with the $-CH_2OH$. The stereochemistry at the new asymmetric center next to the hemiacetal group is tentative but is assigned on the basis of a probably equatorial orientation of the bulky quebrachidine-bearing substituent.

Treatment of the adduct **24** with boron trifluoride etherate at 0° for 6 hr gave alstonisidine, indistinguishable from authentic material. No other compounds were detected, no reversion to starting materials was

(20) N. J. Leonard and J. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).
(21) N. J. Leonard and A. S. Hay, *J. Amer. Chem. Soc.*, **78**, 1984 (1956); N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, 77, 1552 (1955).
(22) B. R. Baker and M. Querry, *J. Org. Chem.*, **15**, 413 (1950).
(23) A. Cope, E. Burrows, M. Devieg, S. Moon, and W. D. Wirth, *J. Amer. Chem. Soc.*, **87**, 5452 (1965).

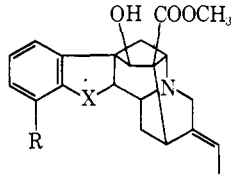
(24) Reaction of methyl vinyl ketone with quebrachidine and reduction with sodium borohydride gave two compounds, as yet incompletely characterized, molecular weight 406, which on the basis of their nmr and identical mass spectra are regarded as the diastereomeric lilolidine analogs i. The nmr spectra in the aromatic region were



very similar to that of 6-methyllilolidine and different from that of 4-methyllilolidine. Further work is in progress.

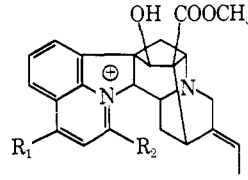
seen, and mixing macroline and quebrachidine with boron trifluoride etherate caused no reaction. This proves that alstonisidine has the structure **25**, which would arise by generation of an oxygen-stabilized carbonium ion from the hemiacetal group and attack of this on the ring. The stereochemistry at the new ring junction is uncertain, but a trans fusion with α-CH_3 and β-H is likely. Crystallographic work presently in progress will settle this point.

The new structure **25** is compatible with the data adduced earlier in support of the isomeric structure **7**. The lithium aluminum hydride reduction to a triol, earlier regarded as indicating an aminoacetal function, as in villalstonine (**1**),[4] is consonant with a tertiary benzylic ether.[25] The mass spectral data[11] are also consistent with structure **25**, although the initial cleavage on electron impact at 325° is not a retro-Diels–Alder reaction but involves bond cleavage and hydrogen migration. The ion assigned[11] structure **26** is actually **27**, and the earlier **28** is **29**. Their origins from **25** are not exceptional.



26, R = CH_2; X = $>\overset{+}{N}$-H

27, R = H; X = $>\overset{+}{N}$=CH_2

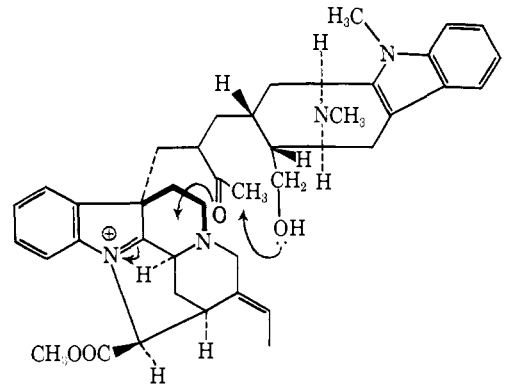


28, R_1 = H; R_2 = CH_3

29, R_1 = CH_3; R_2 = H

This synthesis of alstonisidine, taken together with the unequivocal data obtained from the model compounds, is a proof of structure, as well as of stereochemistry at all but two asymmetric centers. It has two important corollaries: first, that no qualitatively unusual enzymic intervention is necessary for the *in vivo* elaboration of the bisindole alkaloid from "monomeric" precursors; and secondly, that this being so, macroline (**3**) must be regarded as a highly likely biogenetic precursor, even though it may be present in the plant in only small steady-state concentrations. Accordingly we investigated the synthesis of villalstonine (**1**) using the same experimental conditions. Mixing pleiocarpamine (**2**) and macroline (**3**) in 0.2 *N* aqueous hydrochloric acid at 20°. for 18 hr gave villalstonine, indistinguishable from authentic material, as the only product. No intermediates were detected. We believe that the initial reaction, as suggested by Schmid,[4] is an electrophilic addition of the enone function of macroline to the sterically less hindered α face of pleiocarpamine to give a labile intermediate (**30**), which is favorably oriented for an extremely rapid generation of the acetal–aminoacetal systems of villalstonine. This latter part of the reaction sequence could involve a hemiacetal derived from **30** attacking the indoline iminium ion,[4] or indeed may be concerted. Villamine (**31**) with 0.2 *N* aqueous hydrochloric acid was not converted to villalstonine. The generation of the two new rings and four asymmetric centers of villalstonine from the precursors under such simple conditions is again compelling presumptive evidence that these reactions are

(25) Some comparable hydrogenolyses are cited in L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.*, 72, 3586 (1950); B. Witkop and J. B. Patrick, *ibid.*, 74, 3855, 3861 (1952).



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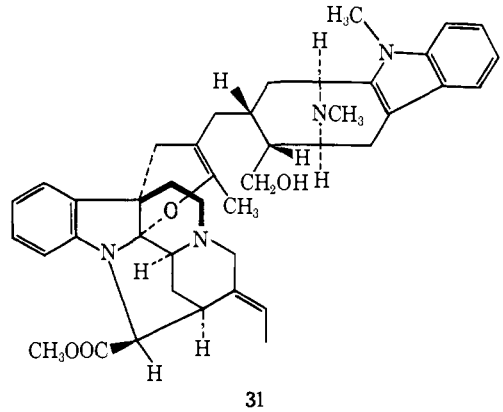

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truly biomimetic and simulate the actual biosynthetic pathway.

These syntheses are to our knowledge the first of any kind among *Alstonia* bisindole alkaloids. They are also interesting, as stated above, in that they show that the biogenesis of the complex structural and stereochemical features of the new rings and asymmetric centers can be accounted for purely in terms of chemical asymmetric induction without involving "special" biochemical phenomena. Further work in this area is in progress.

Experimental Section

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in a Thomas–Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian A-60, A-60A, T-60, and HA-100 spectrometers. Infrared spectra were taken on Perkin-Elmer 237 and Beckman IR-9 instruments. Vpc data were obtained with a Varian Aerograph Model 90-P instrument (thermal conductivity detector) with a 0.25 in. × 6 ft, 20% SE-30 on Chromosorb W column. Ultraviolet spectra were taken on Perkin-Elmer 202 or Cary 14 spectrophotometers and mass spectra on Finnigan 1015 or A.E.I. MS-902 instruments. Analytical tlc plates used were E. Merck–Brinkmann uv-active aluminum oxide on aluminum, and E. Merck–Brinkmann or Eastman uv-active silica gel on plastic. Preparative tlc plates were E. Merck–Brinkmann 2-mm uv-active aluminum oxide on glass and the same brand of uv-active 2-mm and 0.5-mm silica gel on glass. The spray reagent was a saturated solution of cerium(IV) sulfate in 50% aqueous sulfuric acid.

Reactions of *N*-Methylaniline with Methyl Vinyl Ketone. (a) In Acetic Acid. To a mixture of redistilled *N*-methylaniline (Aldrich, 10.7 g, 0.1 mol), water (5 ml), acetic acid (0.5 ml), and hydroquinone (0.1 g), methyl vinyl ketone (Aldrich, 4 g of 85%, 0.05 mol) was added dropwise during 20 min at 60°, with occasional cooling in an ice bath to keep the reaction below 65°. After 1 hr at 60° the reaction was made basic with ammonia and extracted with chloroform. The organic layer was dried (sodium sulfate), the solvent removed, and the oily product distilled at 2 mm. *N*-Methylaniline (4.8 g) distilled at 62–65°, and at 134–138° 4-(*N*-

methylanilino)-2-butanone (**11**) (8.0 g) was obtained, having identical spectral properties with those reported.[26] No other products were detected.

(b) In Aqueous Sulfuric Acid. When the reaction was run exactly as above except that sulfuric acid (0.5 ml) was substituted for the acetic acid, the same products, in the same yields, were obtained.

(c) In Water–Sulfur Dioxide. To a mixture of *N*-methylaniline (10.7 g, 0.1 mol), water (10 ml), and hydroquinone (0.1 g), sulfur dioxide (0.2 g) was added. The temperature rose to 60°, and methyl vinyl ketone (8 g of 85%, 0.1 mol) was introduced during 50 min, the temperature being held at 64°. Work-up as in (a) above gave an oil which deposited long needles on standing. These were filtered off, washed with cold methanol and dried *in vacuo* at 20° (silica gel). This product was identified as 4,4′-bis(2-butanone) sulfone (**12**): mp 114.5–116°; ir ν^{KBr} 1710 (–C=O), 1318, 1140 (S=O) cm^{-1}; nmr δ^{CDCl_3} 2.2 (6 H, s, $COCH_3$), 3.15 (8 H, 4 equal intensity absorptions, A_2X_2 approaching A_2B_2). *Anal.* Calcd for $C_8H_{14}SO_4$: C, 46.68; H, 6.84; S, 15.53. Found: C, 46.60; H, 6.82; S, 15.53.

The mother liquor from the filtration contained only *N*-methylaniline (ir, nmr).

(d) With Aluminum Chloride. Methyl vinyl ketone (10.7 g, 0.1 mol) was added during 30 min to a slurry of *N*-methylaniline (10.7 g, 0.1 mol), dichloromethane (200 ml), and aluminum chloride (30 g), maintained at −10°. The mixture was then allowed to warm to 20° gradually and stirred for 90 min. The aluminum chloride was decomposed with dilute hydrochloric acid and the solution made basic (sodium hydroxide) and extracted with chloroform. The organic layer was dried (magnesium sulfate) and the solvent removed under reduced pressure. Only polymeric material was observed.

When the same reaction was performed in nitrobenzene at 90°[27] essentially the same result was obtained, except that, in addition to the polymeric material, small amounts of unpolymerized starting materials were obtained.

Reaction of Methyl Vinyl Ketone with *N*-Methylacetanilide.[28] Methyl vinyl ketone (7 g) was added during 9 min to a mixture of *N*-methylacetanilide (6.85 g), carbon disulfide (150 ml), and aluminum chloride (20 g) kept at 5° in an ice bath. After the addition, the mixture was allowed to stir at 20° for 3 hr and worked up as above. *N*-Methylacetanilide was isolated together with polymeric material.

Under the same conditions benzene was alkylated to benzylacetone,[17] identified by comparison of its physical properties with those of authentic material.[29]

4-(*N*-Indolinyl)-2-butanone (15). Methyl vinyl ketone (0.7 g, 0.01 mol) was added dropwise to a solution of indoline (1.19 g) in aqueous hydrochloric acid (1 *N*, 20 ml) and the mixture stirred at 20° for 35 min. After the mixture was made basic with ammonia, it was extracted with chloroform, the organic layer dried (magnesium sulfate), and solvent removed under reduced pressure. The resulting slightly brown oil (1.7 g; 95%) was analytically pure 4-(*N*-indolinyl)-2-butanone (**15**): ir ν^{film} 1710 (CH_3CO of ketone), 1610 (indoline), 745 cm^{-1} (aromatic ortho disubstitution); nmr δ^{CDCl_3} 2.1 (3 H, s, CH_3CO), 2.5–3.4 (8 H, m, methylene protons), 6.2–7.1 (4 H, m, aromatic protons); mass spectrum *m/e* 190 (3), 189 (15) M$^+$, 146 (3), 145 (2), 144 (4), 133 (11), 132 (100), 130 (13), 118 (6), 117 (17), 105 (4), 103 (4), 91 (9), 90 (5), 89 (5), 79 (4), 77 (9.5). *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.18; H, 7.93; N, 7.40. Found: C, 76.35; H, 8.01; N, 7.39. Tlc showed the presence of extremely small traces of indoline and of another unidentified compound in the reaction mixture.

Retro-Michael Reaction of 4-(*N*-Indolinyl)-2-butanone (15). The β-amino ketone **15** (1 g) was heated under reflux with acetic anhydride (2 ml) and pyridine (2 ml) for 3 hr. After volatile material had been removed at 20° and 1 mm, the oily residue partially crystallized. The solid material was filtered off, washed with cold methanol, and identified as *N*-acetylindoline (0.5 g): mp 103–104° (ref 30 quotes 103–104°); ir ν^{KBr} 1660 (amide C=O), 750 cm^{-1} (aromatic ortho disubstitution); nmr δ^{CDCl_3} 2.2 (3 H, s, $-COCH_3$), 3.2 (2 H, t, J = 8.4 Hz), 4.1 (2 H, t, J = 8.4 Hz), 6.9–7.2 (3 H, m, aromatic), 8.15 (1 H, d, J = 9 Hz, C-7 aromatic H). From the mother liquor, a trace of 4-acetoxy-2-butanone (**20**, X = CH_3COO) was isolated and identified by nmr spectroscopy.

6-Methyllilolidine (16) from Indoline and Methyl Vinyl Ketone. Methyl vinyl ketone (7.0 g, 0.1 mol) was added dropwise to a solution of indoline (11.9 g, 0.1 mol) in aqueous hydrochloric acid (1 *N*, 100 ml). The solution was stirred at 20° for 3 days and then held at 90° for 6 hr and 60° for 12 hr. Work-up *via* making it basic with ammonia, extraction with chloroform, and concentration of the dried (magnesium sulfate) organic layer gave an oil, which tlc (SiO_2 gel, chloroform) and vpc showed to contain three components. Indoline (R_f 0.52: color with Ce(IV) orange-brown) was present in up to 21% overall yield and was identified by vpc and tlc comparison with authentic material. The second component (up to 43%) was obtained by distillation (bp 82–85° (0.26 mm)) and was 6-methyllilolidine (**16**): R_f 0.59; color with Ce(IV) light orange → dark orange; ir ν^{film} 1610 (indoline), 755 cm^{-1} (aromatic ring), no N–H; nmr δ^{CDCl_3} 1.2 (3 H, d, J = 7 Hz, >$CHCH_3$), 1.85 (2 H, m), 2.5–3.4 (7 H, m), 6.35–7.05 (3 H, aromatic); irradiation of δ 2.5–3.4 caused the CH_3 doublet to collapse to a singlet; mass spectrum *m/e* 174 (6), 173 (M$^+$) (50), 172 (30), 159 (13), 158 (100), 157 (11), 156 (21), 154 (8), 144 (8), 143 (15), 131 (7), 130 (45), 128 (10), 118 (7), 117 (7), 115 (18), 103 (8.5), 91 (14), 90 (5), 89 (9). *Anal.* Calcd for $C_{12}H_{15}N$: C, 83.25; H, 8.66; N, 8.09. Found: C, 83.38; H, 8.75; N, 8.03. This compound with excess methyl iodide under reflux gave a crystalline methiodide, purified for analysis by one recrystallization from acetone, mp 175.5–178°. *Anal.* Calcd for $C_{13}H_{18}NI$: C, 49.49; H, 5.72; N, 4.44; I, 40.25. Found: C, 49.47; H, 5.70; N, 4.52; I, 40.26. The third component of the reaction mixture, obtained in up to 20% yield, was the uncyclized β-amino ketone **15**.

This reaction was repeated several times, the individual yields of the products being somewhat variable. A reaction time of 1 hr at 90° was sufficient to produce 33% 6-methyllilolidine (**16**). No other reaction products, in particular indole, were identified.

***N*-(3-Chlorobutyryl)indoline (17).** 3-Chlorobutyryl chloride (28.2 g, 0.2 mol, from Aldrich's 3-chlorobutyric acid and thionyl chloride) was added during 5 min to a solution of indoline (23.8 g, 0.2 mol) in redistilled acetone (125 ml) under reflux. The solid initially formed redissolved during 1 hr, after which the mixture was cooled and poured into 1 *N* hydrochloric acid (200 ml). The pale orange product was filtered off and recrystallized once from ethanol to give analytically pure *N*-(3-chlorobutyryl)indoline (**17**) (35.4 g, 79%): mp 86–87.5°; ir ν^{KBr} 1660 (amide –C=O), 1600 (indoline), 775 cm^{-1} (aromatic); nmr δ^{CDCl_3} 1.52 (3 H, d, J = 7 Hz, CH_3); 2.68 (2 H, AB_q, resembling triplet, C-2′ H), 3.0 (2 H, t, J = 8.4 Hz, C-2 methylene), 3.85 (2 H, t, J = 8.4 Hz, C-3 methylene), 4.55 (1 H, sextuplet, J = 7 Hz, 3′ H), 7.0 (3 H, C-4,5,6 aromatic protons), 8.18 (1 H, d, C-7 aromatic H). *Anal.* Calcd for $C_{12}H_{14}NClO$: C, 64.50; H, 6.27; N, 6.27; Cl, 15.92. Found: C, 64.77; H, 6.20; N, 6.17; Cl, 15.90.

6-Methyl-4-oxolilolidine (18). An intimate mixture of the chloroamide **17** (14 g) and aluminum chloride (30 g) was heated over a small flame until evolution of hydrogen chloride ceased (20 min). The melt was cooled, and excess aluminum chloride decomposed by addition of an ice-cold mixture of concentrated hydrochloric acid (20 ml) and water (500 ml). The solution was then extracted with ether, and the organic layer was dried (sodium sulfate) and concentrated to give the amide **18**. One recrystallization from ethanol gave analytically pure **18** as needles (12 g, 90%): mp 108–111°; ir ν^{KBr} 1674, 1650 (amide C=O), 1595 (indoline), 1480, 1401 cm^{-1}; nmr δ^{CDCl_3} 1.3 (3 H, d, J = 8.4 Hz, CH_3), 2.2 (1 H, d, J = 8.4 Hz), 4.0 (2 H, t, J = 8.0 Hz), 7.0 (3 H, s, aromatic); mass spectrum *m/e* 187 (46.7, M$^+$), 172 (100), 158 (4.2), 154 (13.3), 145 (10.4), 144 (38), 143 (3.8), 130 (9.2), 128 (8.3), 118 (8.3), 117 (24.0), 116 (8.3), 115 (23.0), 103 (4.1), 102 (4.1), 91 (13.0). *Anal.* Calcd for $C_{12}H_{13}NO$: C, 77.01; H, 6.95; N, 7.49. Found: C, 76.94; H, 6.92; N, 7.45.

6-Methyllilolidine (16) from the Amide 18. Lithium aluminum hydride (10 g) was added to a solution of the amide **18** (10 g) in dry ether (100 ml). After the initial vigorous reaction had subsided, the mixture was heated under reflux for 12 hr, then cooled in an ice bath, and cautiously quenched with water (70 ml). Aluminum salts were dissolved with sodium hydroxide solution (25%, 200 ml), and the solution was extracted with chloroform. The organic layer was dried (sodium sulfate) and concentrated to give 6-methyllilolidine (8.3 g, 90%), of identical physical and spectral properties with that obtained above.

***N*-*sec*-Butylindoline (22, X = H) from Indoline Perchlorate and**

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(27) E. H. Woodruff, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 581.

(28) J. L. Leiserson and A. Weisberger, in ref 27, p 183; F. E. Ray and G. Rieveschl, Jr., ref 27, p 23.

(29) G. Harries and G. Müller, *Ber.*, **35**, 966 (1902).

(30) T. Lesiak, *Rocz. Chem.*, **37**, 499 (1963).

2-Butanone. Indoline perchlorate was prepared by adding perchloric acid (70%, 1:1 in ethanol) to indoline (23.8 g, 0.2 mol) in ether (100 ml) until the solution was just acid to Congo red. A few more drops of indoline were added, and the mixture was held at 20° overnight. The crystalline product was filtered off and purified for analysis and further work by one recrystallization from 2-propanol–ether to give light pink needles (40.3 g): mp 113–116°; ir ν^{KBr} 2800–2300 (quaternary amine salt), 1160–1030 (three bands, perchlorate Cl–O), 750 cm^{-1} (aromatic ortho disubstitution). *Anal.* Calcd for $C_8H_{10}NClO_4$: C, 43.75; H, 4.01; N, 6.38; Cl, 16.19. Found: C, 43.54; H, 4.15; N, 6.31; Cl, 16.23.

2-Butanone (3.6 g, 0.05 mol) and indoline (2 drops) were added to indoline perchlorate (5 g, 0.025 mol) in dry benzene (50 ml), and the mixture was heated under reflux (Dean–Stark trap). After 1.5 hr the molar equivalent of water (0.45 g, 0.025 mol) had been collected and the initially two-phase system had become a suspension of the crystalline iminium perchlorate (6.5 g, 95% yield; ir ν^{KBr} 1638 cm^{-1}, C=N⁺ of iminium salt). This was immediately reduced as described below.

Sodium borohydride (8 g) was slowly added to a solution of the iminium salt (4 g) in ice-cooled dry ethanol (100 ml). The reaction was stirred at 0° for 1 hr, heated under reflux for 1 hr, and worked up by quenching with 5% sodium hydroxide solution (300 ml) and ether extraction. After drying (magnesium sulfate) and removal of ether, *N-sec*-butylindoline (**22**, X = H) remained, pure, as an oil, 2.3 g, 96%: ir ν^{film} 1610 (indoline), 746 cm^{-1} (aromatic); nmr δ^{CDCl_3} 1.00 (6 H, triplet and doublet, CH_3's), 1.3 (2 H, m, $-CH_2-$), 2.6–3.7 (7 H, m, $-CH_2-$), 6.2–7.2 (4 H, m aromatic); mass spectrum *m/e* 175 (M^+, 14), 160 (1.1), 147 (12), 146 (100), 144 (7.0), 131 (8.0), 130 (12), 118 (20), 117 (12), 103 (7), 91 (17), 90 (6.0), 89 (9.0). *Anal.* Calcd for $C_{12}H_{17}N$: C, 82.25; H, 9.70; N, 7.99. Found: C, 82.38; H, 9.80; N, 8.05.

4-Acetoxy-2-butanone from Methyl Vinyl Ketone (*cf.* **ref 31**). A mixture of methyl vinyl ketone (44 g), hydroquinone (0.5 g), acetic acid (120 g), and sodium acetate (6.0 g) was heated under reflux for 11 hr. The solution was cooled to 0° and ether added until the precipitation of sodium acetate was complete. Cold ammonia (14%) was added and the mixture extracted several times with ether. The ether was dried (sodium sulfate) and concentrated to an oil, which was distilled to give 4-acetoxy-2-butanone (bp 67° at 2.5 mm) of identical nmr spectrum with that published.[31] The yield was 28 g (34%); we believe this could be improved by continuous ether extraction of the reaction mixture. Some reversion to starting materials also takes place on distillation, even at 67°.

Reaction of Indoline Perchlorate and 4-Acetoxy-2-butanone. Indoline perchlorate (2.6 g, 0.012 mol), indoline (2 drops), 4-acetoxy-2-butanone (1.56 g, 0.012 mol) and benzene (40 ml) were heated under reflux as described above for the analogous reaction with 2-butanone. Work-up and reduction with sodium borohydride as above gave an oil, which by tlc (SiO_2 gel, 20% dichloromethane in hexane, three developments) contained three compounds: 6-methyllilolidine, indoline, and a minor very polar component, which was not identified. Vpc analysis showed the ratios of these components to be 41:50:9.

When the reaction was performed in acetonitrile instead of benzene and worked up as above, preparative vpc gave 6-methyllilolidine (40%) and *N*-isopropylindoline (40%). Authentic *N*-isopropylindoline was prepared from indoline perchlorate and acetone in acetonitrile, followed by sodium borohydride reduction, as above, except that water was removed from the initial reaction mixture with molecular sieves. Its properties were identical with those published.[32]

Reaction of Indoline Perchlorate with 4-Methoxy-2-butanone. 4-Methoxy-2-butanone was prepared from methyl vinyl ketone as follows. A solution of methyl vinyl ketone (14 g, 0.2 mol) and hydroquinone (0.1 g) in methanol (10 ml) and hydrochloric acid (concentrated, 3 drops) was allowed to stand for 20 min (the temperature rose to 50°) and then was heated under reflux for 8 hr. Distillation gave 4-methoxy-2-butanone (13.5 g, 66%), bp 34° (10 mm). The material had identical properties with those described:[33,34] in addition ir ν^{film} 1715 cm^{-1} (–C=O); nmr δ^{CDCl_3} 2.1 (3 H, ketone CH_3), 2.55 (2 H, t, J = 6 Hz), 3.2 (3 H, s, OCH_3), 3.5 (2 H, t, J = 6 Hz). *Anal.* Calcd for $C_5H_{10}O_2$: C, 58.82; H, 9.81. Found: C, 58.99; H, 9.91.

4-Methoxy-2-butanone (2.04 g, 0.02 mol) was added to indoline perchlorate (4.3 g, 0.02 mol) and indoline (2 drops). A slow reaction took place (yellowish red color), which was furthered by addition of benzene (50 ml) and heating under reflux for 27 hr as above.

The borohydride reduction was performed in acetonitrile solution but was otherwise normal. Preparative vpc of the product gave indoline (15%), *N*-isopropylindoline (61%), and 6-methyllilolidine (17%), as well as two minor components, each approximately 3%, which were not characterized.

Similar results were obtained when molecular sieves and acetonitrile solution were used in the initial reaction. When indoline hydrochloride was substituted for the perchlorate, and when indoline alone was employed, 4-(*N*-indolinyl)-2-hydroxybutane was identified as a major component by tlc (SiO_2 gel, three developments with 20% dichloromethane in hexane; R_f 0.07, Ce(IV) orange-red) and comparison with authentic material (see below). This was prepared by a conventional lithium aluminum hydride reduction of the amino ketone **15** with alkaline work-up as in the reductions above. The product was obtained analytically pure without distillation: ir ν^{film} 3395 (O–H), 1610 (indoline), 750 cm^{-1} (aromatic); nmr δ^{CDCl_3} 1.16 (3 H, d, J = 6 Hz, CH_3CH-), 1.63 (2 H, quintet, J = 7 Hz), 2.5–3.4 (7 H, m), 3.85 (1 H, sextet, H–C–O), 6.3–7.2 (4 H, m, aromatic); mass spectrum *m/e* 192 (2), 191 (M^+, 13), 156 (2), 154 (2), 133 (14), 132 (100), 130 (11.5), 119 (4.6), 118 (8), 117 (17.5), 105 (5), 103 (6), 91 (13.5), 90 (6), 89 (7), 85 (15), 83 (25). *Anal.* Calcd for $C_{12}H_{17}NO$: C, 75.49; H, 8.89; N, 7.33. Found: C, 75.41; H, 8.93; N, 7.41.

4-Methoxy-2-(*N*-indolinyl)butane (**22**, X = OCH_3). 4-Methoxy-2-hydroxybutane was prepared by normal lithium aluminum hydride reduction (acid work-up) of 4-methoxy-2-butanone. It had bp 140° (756 mm) (lit.[35] 145° (760 mm)); nmr δ^{CDCl_3} 1.18 (3 H, d, J = 6 Hz, CH_3CH-), 1.7 (2 H, quartet, J = 6 Hz, C-3 H's), 3.16 (1 H, s, O–H), 3.36 (3 H, s, OCH_3), 3.52 (2 H, t, J = 6 Hz, C-4), 3.94 (1 H, m, J = 6 Hz, C-2 H).

p-Toluenesulfonyl chloride (7.6 g) was added at 0° to a solution of 4-methoxy-2-hydroxybutane (3.15 g) in pyridine (50 ml). After 3 days at 0°, the mixture was poured into ice–water (400 ml) and extracted with ether (2 × 100 ml). The ether extracts were washed with dilute hydrochloric acid (2 × 50 ml of 18%) and then with water (50 ml). After drying (magnesium sulfate), the ether was removed, leaving a pale brown oil which solidified to a white crystalline product during 2 days at 3°. This material, 4-methoxy-2-tosyloxybutane (**23**, X = OCH_3), was used directly below.

Indoline (3.6 g, 0.032 mol) was added to the above methoxytosylate (4.1 g, 0.016 mol) and the mixture stirred at 100° for 7 hr. On cooling the mixture solidified and was broken up with ether; the crystalline indoline tosylate was filtered off. Concentration of the filtrate *in vacuo* gave the 4-methoxy-2-(*N*-indolinyl)butane (**22**, X = OCH_3) (3.20, 98% yield; 97% by vpc) as a slightly brown oil; ir ν^{film} 1609 (indoline), 1120 (–C–O), 745 cm^{-1} (ortho-disubstituted aromatic ring); nmr δ^{CDCl_3} 1.15 (3 H, d, J = 6 Hz), 1.9 (2 H, m), 3.45 (3 H, s, OCH_3), 2.9–4.1 (7 H, m), 6.6–7.5 (4 H, m, aromatic); mass spectrum *m/e* 206 (1.6), 205 (M^+, 10.8), 190 (4.0), 158 (6.3), 147 (11.0), 146 (100), 144 (8.7), 132 (2.4), 131 (3.7), 130 (6.3), 118 (9.8), 117 (7.9), 103 (3.2), 91 (9.5), 90 (3.7), 89 (4.8). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.26; N, 6.83. Found: C, 76.16; H, 9.19; N, 6.73.

4-Methyllilolidine (**19**) (*cf.* **ref 23**). Phosphorus pentoxide (23 g) was added to a mixture of 4-methoxy-2-(*N*-indolinyl)butane (2.2 g, 0.01 mol) and phosphoric acid (20 ml), and the resulting mixture was held at 205° for 7 hr. After cooling, dilution with ice water, and making it basic (sodium hydroxide, 70 ml of 25%), the mixture was extracted with chloroform and the organic layer dried (potassium carbonate) and concentrated to a brown oil (0.7 g, 40%). This was substantially pure 4-methyllilolidine, which was purified for analysis by preparative tlc (silica gel, 1:1 dichloromethane–hexane); ir ν^{film} 1600 (indoline), 755 cm^{-1} (aromatic); nmr δ^{CDCl_3} 1.17 (3 H, d, J = 6 Hz, $-CH-CH_3$), 1.9 (2 H, m), 1.78 (6 H, m), 3.62 (1 H, m), 6.7 (3 H, m, aromatic); mass spectrum *m/e* 173 (M^+, 19.2), 172 (4.2), 159 (12.7), 158 (100), 156 (10.6), 143 (8.5), 131 (4.2), 130 (21.3), 128 (5.3), 117 (4.2), 115 (10.6), 103 (8.5), 102 (4.2), 91 (8.5), 90 (2.1), 89 (4.7). *Anal.* Calcd for $C_{12}H_{15}N$: N, 8.09. Found: N, 7.92.

Villamine (**31**). Trifluoroacetic acid (2 ml) was added during 2

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(34) S. G. Matsolyan, G. A. Chukhadzhyan, and S. A. Vartanyan, *Zh. Obsch. Khim.*, **29**, 451 (1959).

(35) W. Franke and D. Tietjen, German Patent P-962,787 (1957); *Chem. Abstr.*, **53**, 11235*f* (1959).

min with stirring to a solution of villastonine dihydrochloride (1.0 g) in trifluoroacetic anhydride (13 ml) at 20°. After stirring for 10 min more, solvents were removed under reduced pressure at 20°. Crushed ice and excess ammonia were then added and the mixture extracted with chloroform. The organic layer was dried (potassium carbonate) and concentrated. The residue was chromatographed on silica gel (Woelm, activity IV, 13 g) and the column eluted with 1% methanol in chloroform. Analytical tlc (SiO_2 gel, acetone) disclosed three components: unchanged villastonine (R_f 0.36, Ce(IV), purple), villamine (R_f 0.32, Ce(IV), purple), and villoin (R_f 0.15, Ce(IV), purple),[4] which readily reverted to villalstonine on heating or prolonged column chromatography. Those fractions containing mostly villamine were carefully crystallized from the minimum amount of hot acetone: 200 mg of villamine with properties identical in every respect with those recorded[4] were obtained.

Macroline (3). Villamine (510 mg) was dissolved in a little chloroform and by evaporation under N_2 was distributed equally as a film on the inside walls of 38 Pyrex test tubes (10 cm × 13 mm), which had previously been drawn out to give a lower bulb 4 cm long to contain the villamine. The tubes were evacuated to 0.01 mm, sealed off, and placed in batches for 90 sec in an oil bath maintained carefully at 245–250°. After cooling the tubes were broken open and the contents washed out with chloroform. The product was then chromatographed on a 2-mm silica gel preparative tlc plate, and developed twice with acetone. The macroline band (R_f 0.7, Ce(IV), pinkish blue) was excised and the adsorbent extracted at 20° with acetone. Concentration of the acetone extract gave macroline (**3**), recrystallized from ether: mp 207–210° (lit.[4] mp 211–213°) (126 mg, 48%), of properties identical with those described.[4]

Synthesis of the Michael Adduct 24. Quebrachidine (**8**) (52 mg) was dissolved in 0.2 *N* hydrochloric acid (5 ml), and macroline (**3**) (39 mg) was added. After 72 hr of stirring at 20°, the mixture was made basic with ammonia and extracted with chloroform. The chloroform layer was quickly dried (potassium carbonate), concentrated, and chromatographed on a 2-mm preparative SiO_2 gel plate (three developments with acetone). Three bands were seen: two from quebrachidine and macroline, and one very polar one. The most polar band (R_f 0.3, Ce(IV), reddish violet) was excised, powdered, and extracted at 20° with acetone–methanol (1:1) to give the adduct **24** (35 mg) as a foam: ir ν^{KBr} 3570, 3420 (O–H), 1735 cm^{-1} (ester C=O); mass spectrum M^+ *m/e* 690 (calcd for $C_{42}H_{50}N_4O_5$: mol wt, 690); the spectrum run by direct inlet at 250° and 20 eV gave peaks at *m/e* 692 (7), 691 (25), 690 (M^+, 31), 674 (4), 673 (13), 672 (25), 659 (3), 658 (3), 647 (1), 481 (3), 480 (2), 383 (2), 381 (4), 368 (4), 367 (4), 366 (20), 365 (74), 364 (28), 354 (4), 353 (25), 352 (100), 340 (3), 339 (8), 338 (13), 326 (3), 325 (4), 324 (2), 323 (6), 322 (25), 321 (100), 320 (17), 316 (3), 309 (6), 308 (8), 307 (5), 277 (3), 275 (3), 270 (4), 265 (2), 264 (2), 263 (2), 262 (3), 261 (2), 260 (2), 257 (2), 251 (5), 247 (4), 246 (15), 239 (4), 238 (2), 237 (2), 236 (3), 229 (3), 226 (3), 225 (3), 224 (3), 223 (5), 222 (33), 221 (5), 211 (2), 210 (5), 209 (3), 208 (3), 207 (2), 199 (9), 198 (10), 197 (22), 190 (16), 182 (8), 181 (20), 171 (3), 170 (5), 162 (4), 158 (4), 157 (4). The adduct gradually decomposed to macroline and quebrachidine on storage, on treatment with more concentrated aqueous hydrochloric acid, and on tlc alone (acetone–silica gel).

Attempted Reaction of Macroline (3) and Quebrachidine (8) with Boron Trifluoride Etherate. Macroline (**3**) (3 mg) and quebrachidine (**8**) (5 mg) were mixed in a solution of freshly distilled boron trifluoride etherate (0.1 ml) and ether (1 ml) at 0°. After stirring for 6 hr, the mixture was worked up by making it basic with ammonia and chloroform extraction. Analytical tlc (silica gel, acetone) showed only the starting alkaloids; no other compounds were detected.

Cyclization of the Adduct 24 to Alstonisidine (25). The Michael adduct **24** (50 mg) was dissolved in ether (10 ml) and freshly distilled boron trifluoride etherate (1.0 ml), at 0°, and the mixture was stirred for 7 hr. Work-up as above gave a product which analytical tlc (silica gel, acetone) showed to be alstonisidine, with only traces of other unidentified components. This product was chromatographed on a 2-mm preparative silica gel plate (acetone, two developments), and the alstonisidine-containing band was excised and extracted (Soxhlet) with ethyl acetate to give pure alstonisidine as a microcrystalline powdery solid (34 mg): R_f 0.47 (silica gel, acetone) 0.53, (silica gel, benzene 7.75: ethyl acetate 2:diethylamine 0.25), with a cherry-red color with Ce(IV); this behavior was identical with that of authentic alstonisidine. The infrared (KBr) and 100-MHz nmr spectra of the synthetic and authentic alkaloids were superimposable, and the mass spectra (MS-902, run sequentially) were identical; $[\alpha]D$ −144° (*c*, 0.335 in $CHCl_3$) for the synthetic sample; for authentic base $[\alpha]D$ −133° (*c*, 0.208 in $CHCl_3$).

Synthesis of Villalstonine (1). Macroline (**3**) (33 mg) was added to a solution of pleiocarpamine (**2**) (37 mg) in 0.2 *N* aqueous hydrochloric acid (3 ml) and the mixture stirred at 20° for 18 hr. After basification with ammonia, the solution was worked up as above. Analytical tlc (silica gel, acetone) showed that all the macroline had been consumed and that only pleiocarpamine (R_f 0.25, Ce(IV). violet) and villalstonine (R_f 0.39) were present. Villalstonine was isolated by preparative layer chromatography on half a 2-mm silica gel plate (acetone as developing solvent). A narrow band containing pure villalstonine was excised and extracted (Soxhlet) with ethyl acetate. The extract on concentration gave pure villalstonine (25 mg, 38%). The villalstonine obtained was amorphous. It was chromatographically indistinguishable from authentic material in the two systems employed for alstonisidine (R_f 0.63 in benzene 7.75: ethyl acetate 2:diethylamine 0.25, SiO_2 gel). Its 100-MHz nmr spectrum was superimposable on that of authentic material. It had the characteristic ir spectrum (KBr) of amorphous villalstonine,[36] and its spectrum was superimposable on that of a sample of amorphous base prepared by rapid evaporation *in vacuo* at 20° of a freshly prepared chloroform solution of crystalline authentic base.[2a] The amorphous base contains tenaciously held solvent; this is reflected in the $[\alpha]D$ +58° ($CHCl_3$) for the synthetic sample. The authentic crystalline base had $[\alpha]D$ +79° ($CHCl_3$), but the authentic amorphous base, prepared as above and maintained *in vacuo* at 20° for 3 hr, had $[\alpha]D$ +67° ($CHCl_3$).

Stirring 3-mg quantities of either macroline (**3**) or villamine (**31**) in 0.2 *N* aqueous HCl for 6-hr periods led to their quantitative recovery alone and unchanged (tlc, silica gel, acetone).

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(36) R. E. Gilman, Ph.D. Thesis, University of Michigan, 1959.