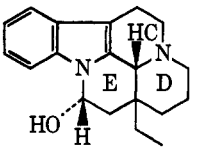
Rearrangement of Benzylidenequinuclidinones to Tetrahydropyridoindoles. A Novel Synthesis of Indole Alkaloids of the Eburnamine Type

D. L. Coffen,* D. A. Katonak, and F. Wong

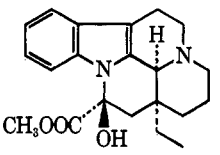
Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received February 15, 1974*

Abstract: A rearrangement reaction has been developed in which *o*-halobenzylidene derivatives of 3-quinuclidinone are converted to tetrahydropyrido[1,2-*a*]indoles. These products possess three of the rings, the two-carbon side chain, and a strategically located ketone function which make them readily amenable to elaboration into the pentacyclic ring system of the eburnamine type alkaloids, as demonstrated with stereoselective total syntheses of *d,l*-dihydroeburnamenine and of *d,l*-epidihydroeburnamenine on a 1-2-g scale.

Eburnamine and vincamine represent a group of indole alkaloids numbering about 15 and sharing a



eburnamine

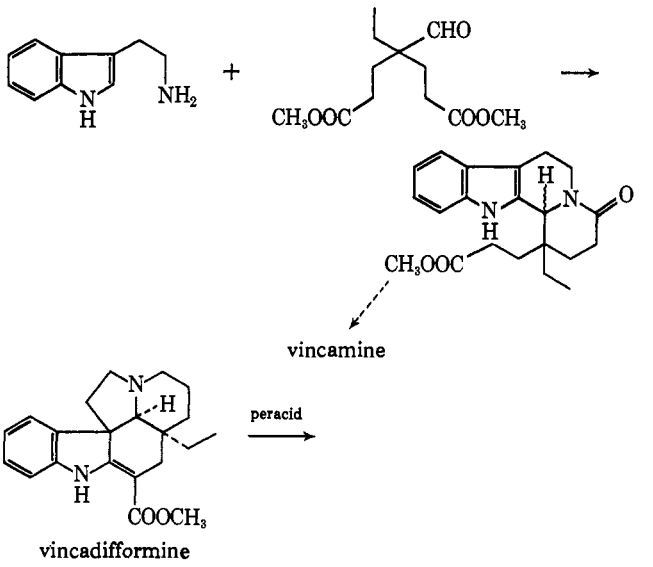


vincamine

common pentacyclic ring system.[1,2] Their various interesting features include physiological activity as cerebral vasodilators.[3] Successful efforts toward the synthesis of these bases began with the structural elucidation studies of Bartlett and Taylor[4] and were continued by research groups directed by Kuehne,[5] Wenkert,[6] Harley-Mason,[7] and Saxton.[8] While differing in their details, these syntheses all utilized, as a basic synthetic strategem, the direct or stepwise condensation of tryptamine with a C_9 or C_{10} unit as exemplified below with a key step from Kuehne's vincamine synthesis.

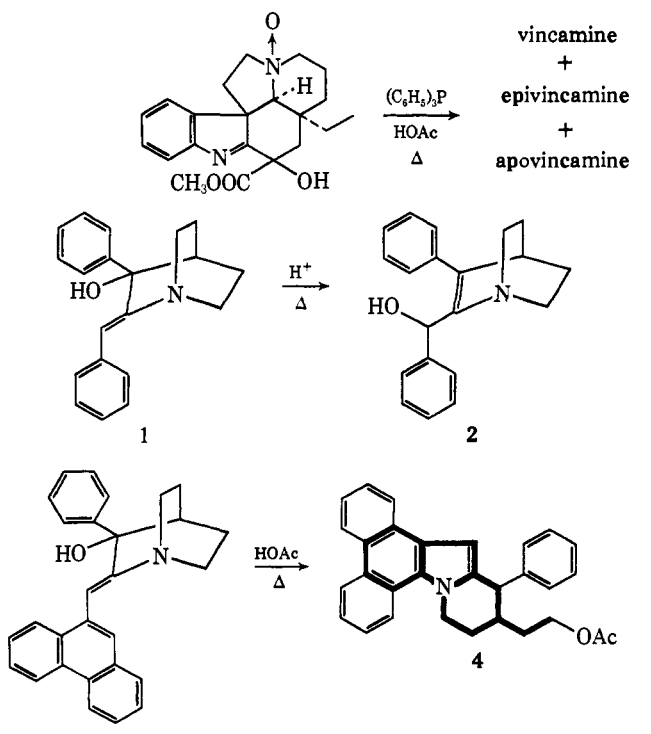
Continuing synthetic efforts along these lines have been the subject of several more recent reports.[9]

The recently reported[10] partial synthesis of vincamine by a reductive rearrangement of a vincadifformine



vincamine

vincadifformine



derivative provides an alternative, probably biomimetic[6] synthetic approach.

(1) W. I. Taylor. *Alkaloids*, **11**, 125 (1968); M. Hesse. "Indolalkaloide in Tabellen," Supplement, Springer-Verlag, New York, N. Y.. 1968, p 45; J. Bruneton, A. Bouquet, and A. Cave, *Phytochemistry*, **12**, 1475 (1973); N. Neuss, H. E. Boaz, J. L. Occolowitz, E. Wenkert, F. M. Schell, P. Potier. C. Kan, M. M. Plat, and M. Plat. *Helv. Chim. Acta*, **56**, 2660 (1973).

(2) A closely related group from Schizozygia caffaeoides has an additional ring formed by attachment of the terminal carbon atom of the side chain to the two position of the indole ring. These have trans-D/E stereochemistry.

(3) M. Aurousseau, *Chim. Ther.*, 221 (1971); M. Aurousseau. M. Dupont, C. Rondeaux, and J. C. Rondeaux, *ibid.*, 234 (1972).

(4) M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, **82**, 5941 (1960).

(5) M. E. Kuehne. *J. Amer. Chem. Soc.*, **86**, 2946 (1964); *Lloydia*. 27, 435 (1964).

(6) E. Wenkert and B. Wickberg. *J. Amer. Chem. Soc.*, **87**, 1580 (1965).

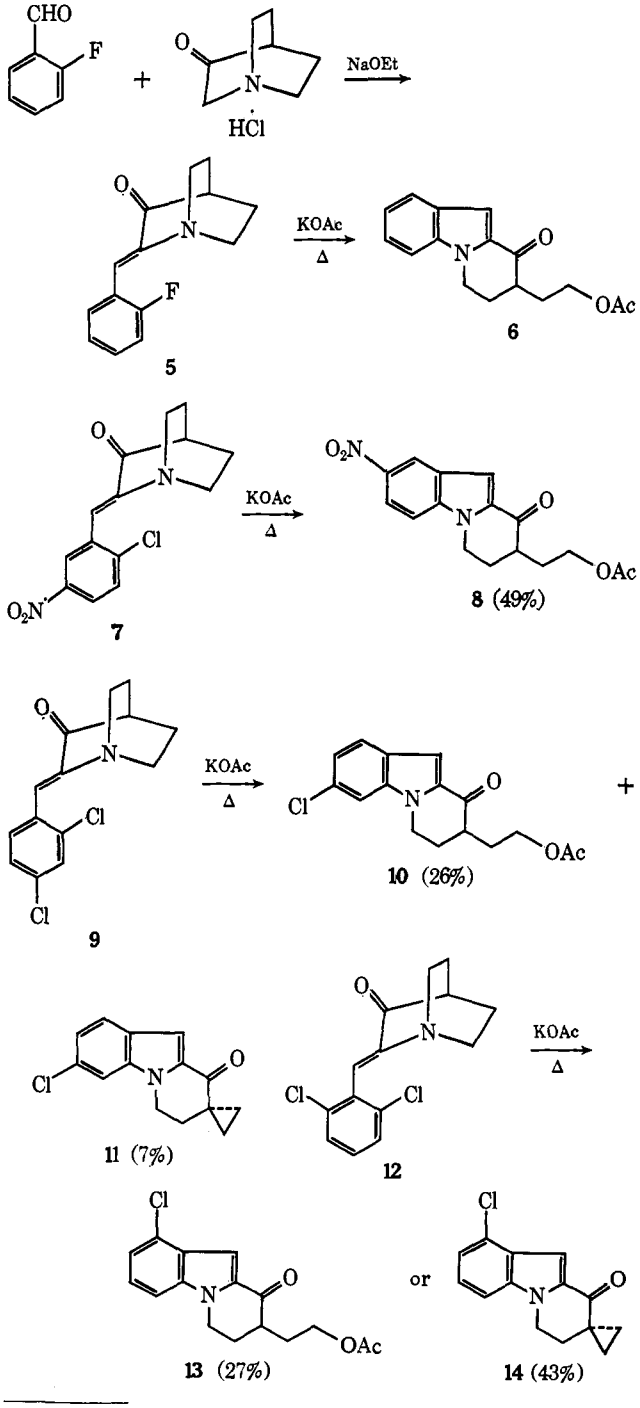
(7) J. E. D. Barton and J. Harley-Mason, *Chem. Commun.*, 298 (1965).

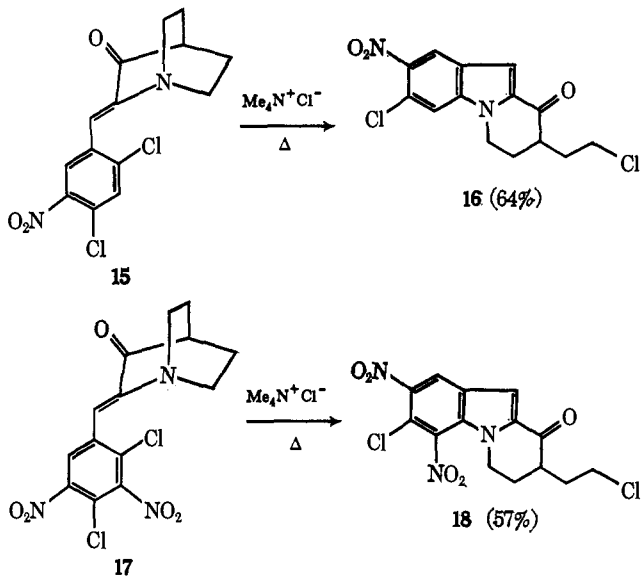
(8) K. H. Gibson and J. E. Saxton. *Chem. Commun.*, 799, 1490 (1969); *J. Chem. Soc., Perkin Trans. 1*, 2776 (1972).

(9) C. Thal. T. Sevenet, H. P. Husson. and P. Potier. *C. R. Acad. Sci., Ser. C*, **275**, 1295 (1972); H. P. Husson. L. Chevolot. Y. Langlois. C. Thal. and P. Potier. *J. Chem. Soc., Chem. Commun.*, 930 (1972); Atta-ur-Rahman, *J. Chem. Soc., Perkin Trans. 1*, 731 (1972); Angence Nat. Val. Rech., Belgium Patent 764116 (1971); Roussel-Uclaf. Belgium Patent 776337 (1972); C. Szántay, L. Szabo. and G. Kalaus, *Tetrahedron Lett.*, 191 (1973); C. Thal. T. Imbert, H. P. Husson, and P. Potier, *Bull. Soc. Chim. Fr.*, 2010, 2013 (1973).

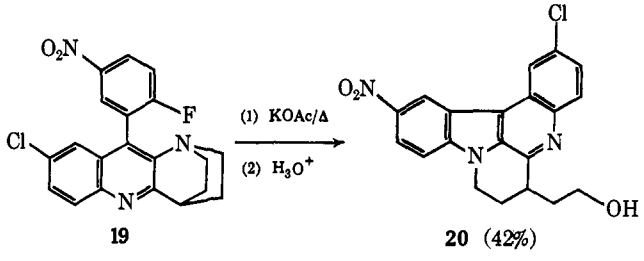
(10) G. Hugel, J. Levy. and J. LeMen, *C. R. Acad. Sci., Ser. C*, 274, 1350 (1972).

A completely different approach to *total* synthesis is embodied in the rearrangement of benzylidenequinuclidinones to tetrahydropyridoindoles, a reaction discovered fortuitously during work on antimalarials of the phenanthrenemethanol class.[11] Since compound **1** undergoes simple allylic rearrangement to alcohol **2** upon treatment with acid,[12] the same behavior was expected of **3**. Instead it undergoes a major skeletal reorganization leading to the tetrahydropyridoindole **4**.[11] The portion of **4** drawn in boldface illustrates the potential utility of this rearrangement in an eburnamine type alkaloid synthesis. In order to realize this potential, the rearrangement was streamlined to provide a product in which functional groups were optimized for subsequent structural elaboration (*i.e.*, **5** → **6**). The reactions for formation and rearrangement of **5** proceed in yields of 90 and 75%, respectively. Some additional examples of this indole synthesis are listed below. Yields are indicated in parentheses.

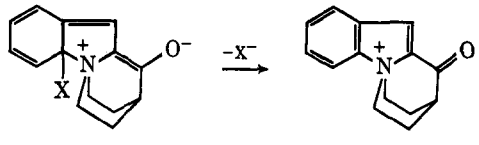




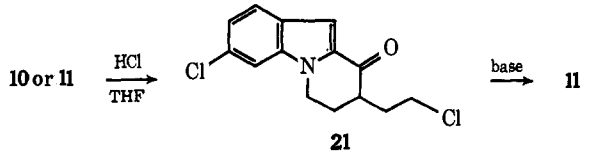
Precisely the same type of rearrangement occurs when the quinuclidine derivative **19** is heated with potassium acetate.[13]



The pathway *via* which these rearrangements proceed probably involves the intermediates shown below. In



those cases involving chlorine as the displaced ortho substituent, the resulting chloride ions may compete with acetate ions as nucleophiles for the ring opening of the quaternary cation. The resulting chloroethyl ketones can then suffer 1,3 elimination leading to cyclopropyl ketones. Such a genesis for compound **11** gains some credibility from the fact that the chloroethyl compound **21** does yield **11** on treatment with various bases.



With compounds **13** and **15**, it was found expedient to have chloride ion as the only nucleophile in the system.

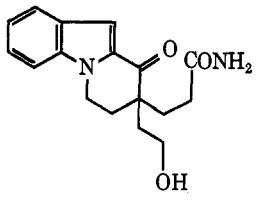
(11) D. R. Bender and D. L. Coffen, *J. Heterocycl. Chem.*, **8**, 937 (1971).

(12) D. L. Coffen and D. G. Korzan, *J. Org. Chem.*, **36**, 390 (1971).

(13) Details of the preparation and rearrangement of **19** and related compounds will be published separately: D. L. Coffen and F. Wong, *J. Org. Chem.*, in press.

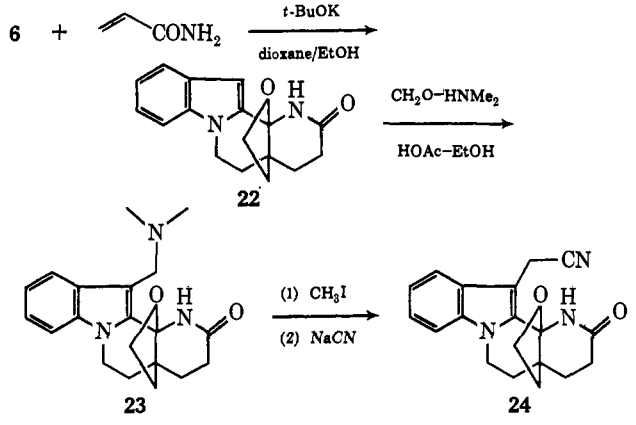
The presence of a second, activated chlorine atom results in complications with acetate ion present.

The annelation of ring D of the eburnamine ring system onto intermediate **6** was accomplished in a single step as shown.[14]

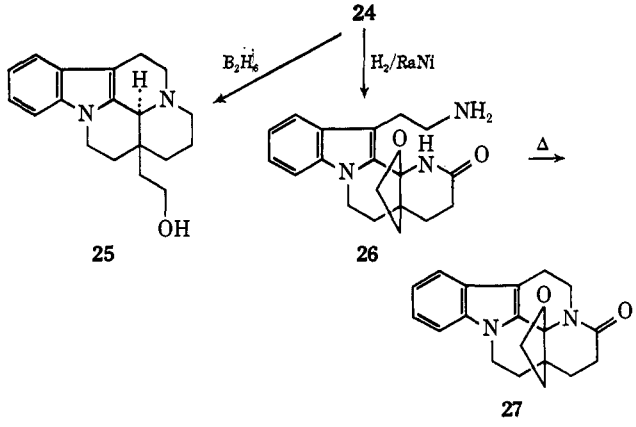


a

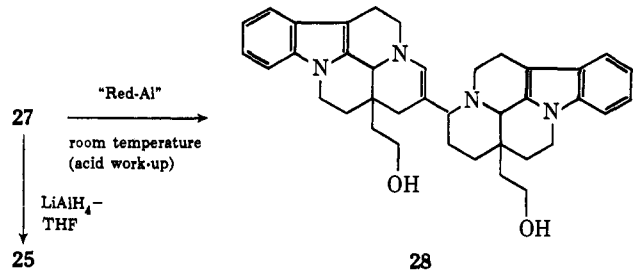
The resulting product **22** initially evaded all efforts to



fuse ring C into place in an equally direct manner and instead an efficient sequence through Mannich base **23** and nitrile **24** was developed (operationally the conversion of **23** to **24** is a single step). A more direct construction of ring C was developed subsequently and is described below.



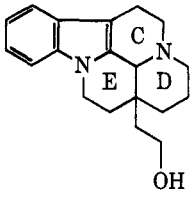
Reduction of nitrile **24** with diborane leads directly to **25**, a substance possessing the eburnamine ring system. Alternatively **24** can be selectively reduced by hydrogenation to **26** which cyclizes to hexacyclic lactam **27** on heating. Metal hydride reduction of **27** also produced **24** or the dimeric base **28**, depending on the vigor of the reduction conditions.[15]



At this point it became necessary to evaluate the stereochemistry of compound **25** in relation to the stereochemistry of the natural bases. The D/E-ring junctures of the latter have been uniformly assigned cis stereochemistry, based on this assignment for eburnamonine[6] and vincamine,[16] although the initial structure determinations of Bartlett and Taylor included an assumption of trans stereochemistry in this substance.[4]

In addition to the cis or trans possibilities for the D/E-ring juncture of **25**, the quinolizidine type C/D-ring juncture may also be cis or trans. Molecular models permit an analysis of the various possibilities in terms of Bohlmann[17] bands and intramolecular hydrogen bonding and these in turn permit stereochemical assignments on the basis of infrared spectral data (Scheme I). Sharp Bohlmann bands at 2750

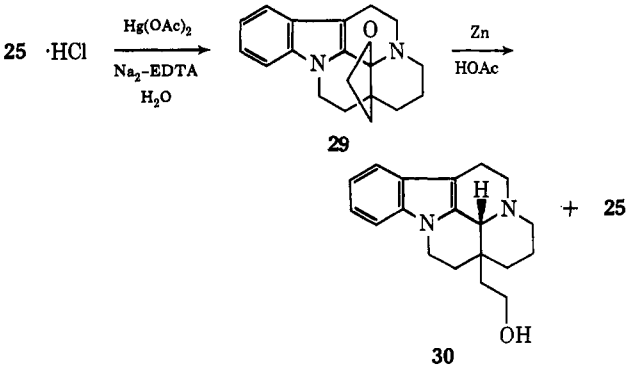
Scheme I



Stereochemistry	C/D-cis, D/E-cis	C/D-cis, D/E-trans	C/D-trans, D/E-cis	C/D-trans, D/E-trans
Bohlmann bands	No	No	Yes	Yes
Intramolecular H bond	Yes	No	No	Yes

and 2830 cm^{-1} together with a concentration-independent OH band at 3300 cm^{-1} in the infrared ($CHCl_3$) spectrum of **25** leads to the assignment of C/D-trans, D/E-trans stereochemistry to this substance.

Epimerization of **25** was accomplished by the oxidation–reduction cycle shown below.



(14) Only the Michael addition proceeds in dioxane as solvent, the cyclizations being blocked by the acetate function. If the reaction is quenched with water and let stand at this stage, the hydrolyzed Michael adduct a can be collected and cyclized to **22** in a separate stage by heating with potassium carbonate in chlorobenzene. In the one-step procedure, ethanol is added to the dioxane solution after 1 hr of reflux and continued heating effects ethanolysis of the acetate and cyclization.

(15) Such imminium ion/enamine dimerizations are not uncommon: *cf.* sparteine, C. Schöpf and K. Keller, *Naturwissenschaften*, **43**, 325 (1956).

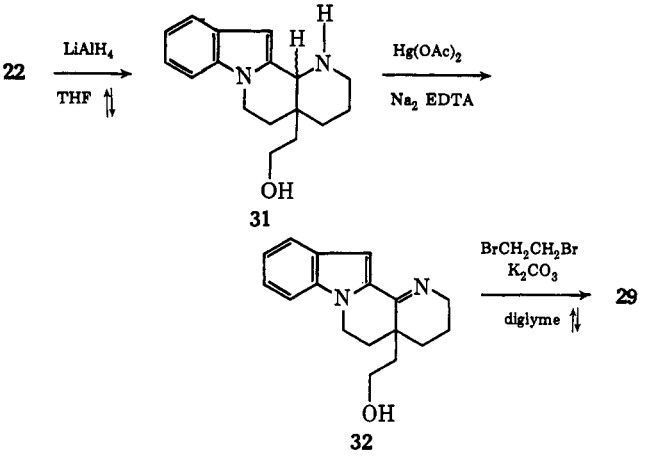
(16) J. Mokry, M. Shamma, and H. E. Soyster, *Tetrahedron Lett.*, 999 (1963).

(17) The utility of Bohlmann bands in assigning stereochemistry to such indoloquinolizidines is nicely demonstrated in a recent study by G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, **38**, 2831 (1973).

The conversion to **29** using Knabe's conditions[18] proceeded cleanly and in excellent yield. This substance forms yellow solutions in acid and stirring of an acetic acid solution with zinc dust causes fading of the color and production of compound **30**, together with variable amounts of **25**.[19] Compound **30** shows clear-cut evidence of intramolecular hydrogen bonding but no well-defined Bohlmann bands in its infrared spectrum. It is thus assigned the C/D-cis, D/E-cis stereochemistry. Its mass spectrum is, of course, nearly identical with that of **25**, differing only in the intensity of a peak at *m/e* 226.

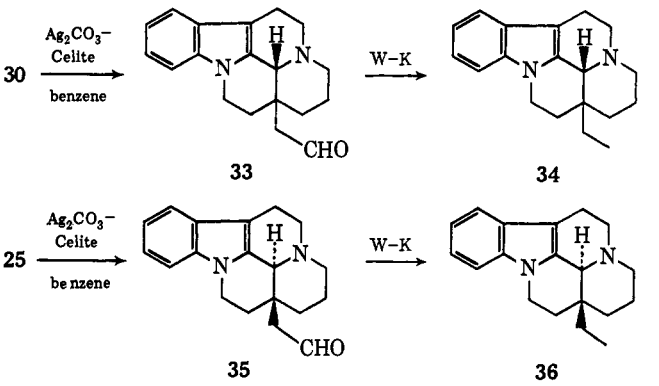
These stereochemical assignments were correlated with ^{13}C nmr data for the two compounds utilizing analogies from the yohimbine alkaloid shift data of Cochran and Wenkert[20] and of Roberts and coworkers.[21] The ^{13}C nmr spectra of several alkaloids of the yohimbine and related types compiled by these groups revealed a unique dependence of the C_6 chemical shift on the stereochemistry at C_3 (*vis-à-vis* the stereochemistry of the C/D-ring juncture). The signal for this carbon atom is the highest field signal in the spectra of most alkaloids examined. It generally falls in the range 16–18 ppm (downfield from TMS) with a β proton at C_3 (C/D-cis series) and in the range 21–23 ppm with an α proton at C_3 (C/D-trans series). The highest field signals in compounds **30** and **25** appear at 17.3 and 21.2 ppm, respectively. Similarly the ^{13}C spectra of dihydroeburnamenine (**34**) and of its C_3 epimer (**36**) contain signals at 17.3 and 18.7 ppm; the next to highest field signals for these compounds as the *C*-methyl groups appear at 7.6 and 7.3 ppm. The signal assigned to C_3 in the trans isomer (18.7) is outside the expected range but still clearly at lower field than in the cis isomer.[22]

Compound **25** is in two respects an unfortunate intermediate, its formation from **24**, albeit highly stereoselective, proceeds in poor yield (25%) and leads to the unnatural epi series. Efforts to improve the synthesis by circumventing **25** produced the more direct route from **22** to **29** shown below. *Via* this sequence **29** is



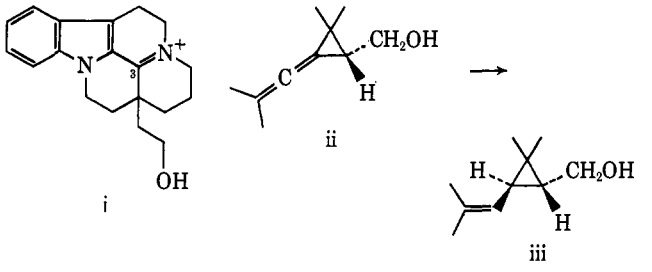
prepared in six instead of seven steps and the lowest yield step (**32** → **29**) proceeds in 61% yield. The relative stereochemistry of **31** has not been determined. The tetracyclic imine structure of **32** is assigned rather than the pentacyclic alternative on the basis of its spectral properties.

A point of convergence with substances of natural origin was reached by removal of the alcohol function from compound **26** to produce *d,l*-dihydroeburnamenine (**34**).[23] Of the two reasonable methods for effecting this transformation, metal hydride hydrogenolysis of a corresponding halide or tosylate was precluded by a propensity for internal quaternization[25] of the basic nitrogen atom. The other method, oxidation to an aldehyde followed by Wolff–Kishner reduction, proceeded satisfactorily once it was found that silver carbonate on Celite[26] made the selective oxidation to **33** possible.



Comparison of *d,l*-dihydroeburnamenine with the authentic *l* enantiomer[27] was made using tlc and mass spectrometry by which criteria they are indistinguishable.

Removal of the hydroxyl function from compound **25**



(18) J. Knabe, *Arch. Pharm.*, **292**, 416 (1959); **293**, 121 (1960); J. Knabe and G. Grund, *ibid.*, **296**, 854 (1963); J. Knabe and H. Roloff, *Chem. Ber.*, **97**, 3452 (1964).

(19) The uv spectrum of compound **29**, λ_{max} 230 (35,400) and 286 mμ (7230), shifts in acid to λ_{max} 251 (14,500) and 358 mμ (23,000). This shift can be ascribed to the formation of iminium ion i by analogy with results of H. Fritz and O. Fischer, *Tetrahedron*, **20**, 2047 (1964). Reduction of similar species during the course of Wenkert's synthetic studies[6] produced exclusively trans-D/E products whereas **30** is the major and occasionally the only product in the present instance. This reversal of stereoselectivity could well be a consequence of proton delivery to C-3 by the alkanol side chain, *e.g.*, as proposed to account for stereoselectivity observed in the reduction of ii to iii: R. W. Mills, R. D. H. Murry, and R. A. Raphael. *J. Chem. Soc., Perkin Trans. 1*, 133 (1973).

(20) D. W. Cochran. Ph.D. Thesis, Indiana University, 1971.

(21) R. H. Levin, J.-Y. Lallemand, and J. D. Roberts. *J. Org. Chem.*, **38**, 1983 (1973).

(22) The ^{13}C spectra of these compounds are discussed separately in greater detail: D. L. Coffen and R. Pitcher, manuscript in preparation.

(23) Dihydroeburnamenine is not itself a natural product but is known both as the hydrogenation product of eburnamenine[4] and as a degradation product of the dimeric alkaloid pleiomutin.[24]

(24) D. W. Thomas, H. Achenbach. and K. Biemann, *J. Amer. Chem. Soc.*, **88**, 1537 (1966).

(25) Iboxygaine shows analogous behavior: D. Stauffacher and E. Seebeck, *Helv. Chim. Acta*, **41**, 169 (1958); K. Biemann and M. Friedmann-Spiteller, *J. Amer. Chem. Soc.*, **83**, 4805 (1961); U. Renner and D. A. Prins, *Experientia*, **15**, 456 (1959).

(26) M. Fetizon and M. Golfier, *C. R. Acad. Sci., Ser. C*, **267**, 900 (1968); M. Fetizon, M. Golfier, and P. Mourgues. *Tetrahedron Lett.*, 4445 (1972).

(27) For which we thank Drs. M. F. Bartlett and H. Gschwend of Ciba-Geigy.

by the same procedure provided *d,l*-epidihydroeburnamenine (**36**).

Experimental Section[28]

2-(*o*-Fluorobenzylidene)-3-quinuclidinone (5). A solution of sodium ethoxide in ethanol was prepared by dissolving 30 g (1.3 g-atom) of sodium in 1 l. of ethanol. 3-Quinuclidinone hydrochloride (161.6 g, 1 mol) and *o*-fluorobenzaldehyde (124.1 g, 1 mol) were added in that order and the resulting mixture was heated on the steam bath for 5 min with frequent swirling. Water (4 l.) is added gradually. At first the precipitate of sodium chloride dissolved and then the product began to separate from the clear solution. The product was collected, thoroughly washed with water, and air dried to give 210 g (91%) of yellow solid. An analytical sample from ethanol had mp 118–119°: ir (Nujol) 1700 and 1625 cm^{-1}; nmr ($CDCl_3$) 2.0 (triplet of doublets, 4 H), 2.67 (quintet, 1 H), 3.1 (m, 4 H), 7.2 (m, 3 H, aromatic), 7.35 (s, 1 H, vinyl), and 8.56 (triplet of doublets, 1 H, aromatic); mass spectrum *m/e* 202 (100%) and 231 (M^+).

Anal. Calcd for $C_{14}H_{14}FNO$: C, 72.71; H, 6.11; N, 6.06. Found: C, 72.82; H, 6.11; N, 6.13.

6,7-Dihydro-8-(β-acetoxyethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (6). A mixture of compound **5** (201.5 g) and potassium acetate (201.5 g) in diglyme (1 l.) was heated to reflux with mechanical stirring under an argon atmosphere for 20 hr. The mixture was allowed to cool and then poured over *ca.* 1 l. of crushed ice. The resulting mixture was partitioned between benzene (2 l.) and water. The benzene layer was washed several times with water, dried, treated with charcoal, and evaporated to an oil. This oil was taken up in ether (300 ml) causing the product to crystallize. Two crops totaling 175.4 g (79%) were collected and washed with ice–cold ether. By acid extraction of the mother liquor, 12.2 g of starting material was recovered. The product is obtained as colorless or pale yellow crystals with mp 74–76°: ir (Nujol) 1725, 1680, 1530, and 1260 cm^{-1}; nmr ($CDCl_3$) 2.02 (s, 3 H), 1.5–2.8 (m, 5 H), 4.2 (m and t superimposed, 4 H), 7.3 (m, 4 H), and 7.7 (dd, 1 H); mass spectrum *m/e* 185 (100%) and 271 (M^+).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.65; H, 6.50; N, 4.99.

2-(2-Chloro-5-nitrobenzylidene)-3-quinuclidinone (7). The condensation of 2-chloro-5-nitrobenzaldehyde (135.9 g, 0.73 mol) with 3-quinuclidinone hydrochloride (120 g, 0.745 mol) using sodium (23 g, 1 g-atom) in ethanol (700 ml) as described for compound **5** (heat 30 min) gave 205.2 g (96%) of compound **7**. An analytical sample was recrystallized from ethanol to give yellow crystals with mp 131–132°: ir (Nujol) 1700 and 1625 cm^{-1}; nmr ($CDCl_3$) 2.08 (triplet of doublets, 4 H), 2.72 (quintet, 1 H), 3.1 (m, 4 H), 4.43 (s, 1 H, vinyl), 7.55 (d, 1 H), 8.10 (dd, 1 H), and 9.53 (d, 1 H).

Anal. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.45; H, 4.48; N, 9.57; Cl, 12.11. Found: C, 57.60; H, 4.40; N, 9.62; Cl, 12.03.

2-Nitro-6,7-dihydro-8-(β-acetoxyethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (8). A mixture of compound **7** (28.6 g) and potassium acetate (28.6 g) in diglyme (250 ml) was heated and stirred at reflux under argon for 4 hr. The reaction mixture was worked up as described for compound **6** to give 13.5 g (49%, 3 g of **7** recovered) of compound **8** in pale yellow crystals from ether with mp 151–152°: ir (Nujol) 1740, 1670, 1530, 1515, 1340, and 1250 cm^{-1}; nmr ($CDCl_3$) 2.06 (s, 3 H), 1.6–3.0 (m, 5 H), 4.35 (m and t superimposed, 4 H), 7.44 (d, 1 H), 7.55 (s, 1 H), 8.23 (dd, 1 H), and 8.7 (d, 1 H); mass spectrum *m/e* 230 (100%) and 316 (M^+).

Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.10; N, 8.86. Found: C, 60.72; H, 5.14; N, 8.77.

2-(2,4-Dichlorobenzylidene)-3-quinuclidinone (9). The condensation of 2,4-dichlorobenzaldehyde (87.5 g, 0.5 mol) with 3-quinuclidinone hydrochloride (80.8 g, 0.5 mol) using sodium (15 g, 0.65 g-atom) in ethanol (750 ml) as described for compound **5** (heat 20 min) gave 128.5 g (91%) of compound 9. An analytical sample was recrystallized from methylene chloride–cyclohexane to give yellow needles with mp 117–118°: ir (Nujol) 1700, 1625, and 1580 cm^{-1}; mass spectrum *m/e* 218, 246 (100%), and 281 (M^+).

Anal. Calcd for $C_{14}H_{13}Cl_2NO$: C, 59.59; H, 4.64; N, 4.96; Cl, 25.13. Found: C, 59.66; H, 4.55; N, 4.81; Cl, 24.97.

3-Chloro-6,7-dihydro-8-(β-acetoxyethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (10) and 3′-Chloro-6,7-dihydrospiro(cyclopropane-1,8′-pyrido[1,2-*a*]indol)-9′(8′*H*)-one (11). A mixture of compound **9** (56 g) and potassium acetate (56 g) in triglyme (500 ml) was heated and stirred under reflux in an argon atmosphere for 18 hr. Reaction work-up as described for compound **6** gave an oily mixture of **10** and **11**. This mixture was taken up in ether and stored in the cold to give 15.8 g (26%) of compound **10**. An analytical sample was recrystallized from methylene chloride–cyclohexane in colorless crystals with mp 119–120°: ir (Nujol) 1725, 1600, 1515, and 1230 cm^{-1}; nmr ($CDCl_3$) 2.06 (s, 3 H), 1.4–2.8 (m, 5 H), 4.3 (m and t superimposed, 4 H), 7.10 (dd, 1 H), 7.21 (s, 1 H), 7.33 (d, 1 H, meta coupled), and 7.60 (d, 1 H, ortho coupled); mass spectrum *m/e* 219 (100%) and 305 (M^+).

Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58; Cl, 11.60. Found: C, 62.88; H, 5.42; N, 4.41; Cl, 12.28.

Column chromatography of the mother liquor on silica gel provided 3.5 g (7%) of compound **11** plus some additional compound **10**. **11** crystallized from methylene chloride–cyclohexane in pale yellow crystals with mp 125–126°: ir (Nujol) 1660, 1600, and 1525 cm^{-1}; nmr ($CDCl_3$) 0.90, 1.45 (A, A′, B, B′ multiplets, 4 H), 2.21 (t, J = 6, 2 H), 4.21 (t, J = 6, 2 H), 7.06 (dd, 1 H), 7.20 (s, 1 H), 7.30 (d, 1 H, meta coupled), and 7.60 (d, 1 H, ortho coupled); mass spectrum *m/e* 245 (100%, M^+).

Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.50; H, 5.02; N, 5.53; Cl, 14.58.

2-(2,6-Dichlorobenzylidene)-3-quinuclidinone (12). The condensation of 2,6-dichlorobenzaldehyde (100.2 g, 0.57 mol) with 3-quinuclidinone hydrochloride (93.5 g, 0.57 mol) using sodium (18 g, 0.78 g-atom) in ethanol (750 ml) and 10 hr at reflux gave 149 g (92%) of compound **12**. An analytical sample from methylene chloride–petroleum ether was obtained as yellow crystals with mp 128–130°: ir (Nujol) 1705, 1650, and 1570 cm^{-1}; nmr ($CDCl_3$) 2.0 (triplet of doublets, 4 H), 2.64 (quintet, 1 H), 3.0 (m, 1 H), 7.02 (s, 1 H), and 7.30 (m, 3 H).

Anal. Calcd for $C_{14}H_{13}Cl_2NO$: C, 59.59; H, 4.64; N, 4.96; Cl, 25.13. Found: C, 59.73; H, 4.47; N, 4.95; Cl, 24.80.

1-Chloro-6,7-dihydro-8-(β-acetoxyethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (13). A mixture of compound **12** (44 g), potassium acetate (44 g), and tetramethylammonium chloride (4.4 g) in triglyme (500 ml) was stirred and heated to reflux under argon for 18 hr. Reaction work-up as described for compound **6** gave an oily mixture of compounds **13** and **14**. Crystallization from ether provided 12.7 g (27%) of compound **13**, this being the major product when tetramethylammonium chloride is present during the reaction. An analytical sample from methylene chloride–ether was obtained in colorless crystals with mp 77–78°: ir (Nujol) 1730, 1670, and 1525 cm^{-1}; nmr ($CDCl_3$) 2.05 (s, 3 H), 1.5–3.0 (m, 5 H), 4.35 (m and t superimposed, 4 H), 7.20 (m, 3 H), and 7.35 (s, 1 H); mass spectrum *m/e* 219 (100%) and 305 (M^+).

Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58; Cl, 11.60. Found: C, 62.97; H, 5.16; N, 4.50; Cl, 11.58.

1′-Chloro-6,7-dihydrospiro(cyclopropane-1,8′-pyrido[1,2-*a*]indol)-9′(8′*H*)-one (14). A mixture of compound **12** (95 g) and potassium acetate (95 g) in triglyme (1 l.) was stirred and heated to reflux under argon for 18 hr. Reaction work-up as described for compound **6** provided 56 g of an oily mixture of compounds **13** and **14**. By a combination of fractional crystallization and column chromatography of mother liquors on silica gel, 35.8 g (43%) of compound **14** was obtained as colorless crystals from methylene chloride–ether with mp 118–120°: ir (Nujol) 1665 and 1525 cm^{-1}; nmr ($CDCl_3$) 0.90, 1.50 (A, A′, B, B′ multiplets, 4 H), 2.21 (t, J = 6, 2 H), 4.23 (t, J = 6, 2 H), and 7.0–7.4 (s and m, 4 H); mass spectrum *m/e* 245 (100%, M^+).

Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.22; H, 4.86; N, 5.59; Cl, 14.43.

2-(2,4-Dichloro-5-nitrobenzylidene)-3-quinuclidinone (15). A cold solution of compound 9 (110 g) in concentrated sulfuric acid (500 ml) was treated with potassium nitrate (220 g) in portions while stirring. Stirring was continued for 30 min after completion of the addition and the solution was then poured over crushed ice. Neutralization with aqueous sodium carbonate precipitated the product as a yellow solid. This was collected, washed with water, and taken up in methylene chloride. The dried solution was concentrated with gradual addition of ethanol giving 100 g (78%) of a crystalline mixture of the cis and trans isomers (by tlc and nmr) of compound **15**. An analytical sample obtained by a second recrystallization had mp 121–129°: ir (Nujol) 1715, 1640, 1600, 1550, 1525, and 1335 cm^{-1}; nmr ($CDCl_3$) 2.0 (m, 4 H), 2.75 (m, 1 H), 3.20

(28) Melting points are uncorrected. Nmr spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.

(m, 4 H), and six singlets between 6.8 and 9.4 (3 H); mass spectrum *m/e* 326 (M^+).

Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56; Cl, 21.67. Found: C, 51.19; H, 3.63; N, 8.49; Cl, 21.73.

3-Chloro-2-nitro-6,7-dihydro-8-(β-chloroethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (16). A solution of compound **15** (23 g) and tetramethylammonium chloride (2.3 g) in diglyme (230 ml) was stirred and heated to reflux under argon for 18 hr. Reaction work-up as described for compound **6** and crystallization of the crude product from methylene chloride–petroleum ether gave 14.7 g (64%) of compound **16** in yellow crystals. An analytical sample had mp 132–133°: ir (Nujol) 1675, 1620, 1560, 1530, and 1330 cm^{-1}; nmr ($CDCl_3$–DMSO-d_6) 1.6–3.2 (m, 5 H), 3.75 (t, J = 6.5, 2 H), 4.20 (m, 2 H), 7.23 (s, 1 H), 7.56 (s, 1 H), and 8.22 (s, 1 H); mass spectrum *m/e* 264 (100%) and 326 (M^+).

Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H, 3.70; N, 8.56; Cl, 21.67. Found: C, 51.37; H, 3.50; N, 8.65; Cl, 21.82.

2-(2,4-Dichloro-3,5-dinitrobenzylidene)-3-quinuclidinone (17). A solution of compound 9 (30 g) in concentrated sulfuric acid (300 ml) was treated with concentrated nitric acid (150 ml) and heated on the steam bath for 1 hr. The solution was poured over crushed ice and neutralized with aqueous sodium carbonate. The crude product was collected, washed, dried, and recrystallized from methylene chloride–ethanol giving 17.3 g (44%) of compound **17** in three crops as yellow orange crystals. This compound was obtained as a single isomer by tlc and nmr. An analytical sample had mp 161–163°: ir (Nujol) 1700, 1625, 1580, 1535, and 1335 cm^{-1}; nmr ($CDCl_3$–DMSO-d_6) 1.9–3.5 (quinuclidine multiplets, 9 H), 7.20 (s, 1 H), and 9.52 (s, 1 H).

Anal. Calcd for $C_{14}H_{11}Cl_2N_3O_5$: C, 45.18; H, 2.98; N, 11.29; Cl, 19.05. Found: C, 45.23; H, 2.89; N, 11.23; Cl, 19.49.

3-Chloro-2,4-dinitro-6,7-dihydro-8-(β-chloroethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (18). A solution of compound **17** (9.3 g) and tetramethylammonium chloride (1 g) in diglyme (100 ml) was heated to reflux with stirring under argon for 18 hr. Reaction work-up as described for compound **6** and crystallization of the crude product from methylene chloride–petroleum ether gave 5.3 g (57%) of compound **18** in light yellow crystals. An analytical sample had mp 153–156°: ir (Nujol) 1700, 1630, 1540, and 1360 cm^{-1}; nmr ($CDCl_3$–DMSO-d_6) 1.60–3.40 (m, 5 H), 3.83 (t, 2 H), 4.20 (m, 2 H), 7.55 (s, 1 H), and 8.73 (s, 1 H); mass spectrum *m/e* 309 (100%) and 371 (M^+).

Anal. Calcd for $C_{14}H_{11}Cl_2N_3O_5$: C, 45.18; H, 2.98; N, 11.29; Cl, 19.05. Found: C, 45.18; H, 2.70; N, 11.24; Cl, 19.44.

3-Chloro-6,7-dihydro-8-(β-chloroethyl)pyrido[1,2-*a*]indol-9(8*H*)-one (21). A mixture of compounds **10** and **11** (2 g) in THF (25 ml) was treated with anhydrous hydrogen chloride until the solution was saturated. It was then heated to reflux overnight, cooled, and partitioned between water and methylene chloride. The organic layer was dried, treated with charcoal, and evaporated to an oil. Crystallization from methylene chloride–ether–petroleum ether gave 1.45 g of compound **21** as light tan leaflets with mp 107–109°: ir (Nujol) 1670, 1620, and 1525 cm^{-1}; mass spectrum *m/e* 219 (100%) and 281 (M^+).

Anal. Calcd for $C_{14}H_{13}Cl_2NO$: C, 59.59; H, 4.64; N, 4.96; Cl, 25.13. Found: C, 59.79; H, 4.43; N, 5.09; Cl, 25.13.

6,7,8,9-Tetrahydro-7a,11a-ethanooxyindolo[1,2-*h*][1,7]naphthyridin-10(11*H*)-one (22). A solution of compound **6** (151.3 g, 0.56 mol), acrylamide (32.4 g, 0.59 mol), and potassium *tert*-butoxide (62 g, 0.56 mol) in dioxane (1.5 l.) was stirred and heated under reflux for 1 hr. Ethanol (1.5 l.) was then added, slowly at first, followed by an additional 31 g of potassium *tert*-butoxide. Reflux was continued for 9 hr and then the solvent was evaporated under reduced pressure. The resulting syrup was diluted with water (4 l.) and extracted six times with 1-l. portions of methylene chloride. The residue from the dried extract after evaporation was treated with ether (500 ml) and chilled overnight. The product was filtered, washed with more ether, and dried to give 96.4 g (61%) of compound **22**. An analytical sample was recrystallized from methylene chloride–ether to give colorless crystals with mp 233–234°: ir (Nujol) 3130, 3030, 1650, and 1535 cm^{-1}; nmr ($CDCl_3$–DMSO-d_6) 1.8–2.8 (m, 8 H); 3.8–4.3 (m, 4 H), 6.68 (s, 1 H), 7.0–7.5 (m, 5 H, including NH), and 7.63 (dd, 1 H); mass spectrum *m/e* 282 (100%, M^+).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.47; H, 6.36; N, 9.86.

12-(*N*,*N*-Dimethylaminomethyl)-6,7,8,9-tetrahydro-7a,11a-ethanooxyindolo[1,2-*h*][1,7]naphthyridin-10(11*H*)-one (23). A mixture of compound **22** (20 g), aqueous formaldehyde (20 ml of 37% soln), aqueous dimethylamine (30 ml of 25% soln), and glacial acetic acid (1 ml) in ethanol (200 ml) was stirred under reflux overnight. The resulting clear solution was evaporated under reduced pressure and the solid residue triturated with a small volume of ethanol. The product was collected, washed with water and dried to give 24 g (100%) of colorless compound **23**. An analytical sample from methylene chloride–ether had mp 232–238°: ir (Nujol) 3450 and 1655 cm^{-1}; nmr ($CDCl_3$) 1.8–2.7 (m, 8 H), 2.35 (s, 6 H), 3.0–4.4 (m, 6 H), 7.0–7.8 (m, 4 H), and 10.66 (NH); mass spectrum *m/e* 295 (100%) and 339 (M^+).

Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.78; H, 7.52; N, 12.20.

12-Cyanomethyl-6,7,8,9-tetrahydro-7a,11a-ethanooxyindolo[1,2-*h*][1,7]naphthyridin-10(11*H*)-one (24). A mixture of compound **23** (73.2 g) and methyl iodide (92 ml) in DMSO (150 ml) was heated to 50° on the steam bath for 10 min during which a clear solution of the methiodide formed. Ether (300 ml) was added and boiled off to expel excess methyl iodide. A solution of sodium cyanide (150 g) in water (750 ml) was then added and the resulting solution heated vigorously on the steam bath with occasional swirling for 1 hr. After cooling overnight, the thick precipitate of compound **24** was filtered, washed with water, and air dried to give 64 g (92%) of light yellow powder. Recrystallization from either methylene chloride or DMSO gives colorless crystals with mp 264–266°: ir (Nujol) 3150, 3050, 2250, 1660, and 1570 cm^{-1}; nmr (DMSO-d_6) 1.8–2.7 (m, 8 H), 3.5–4.7 (m, 6 H), 7.3–8.2 (m, 4 H), and 8.6 (s, NH); mass spectrum *m/e* 321 (100%, M^+).

Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.82; H, 6.03; N, 12.87.

***d,l*-Epi-18-hydroxydihydroeburnamenine (25). (a) Hydrochloride.** A slurry of compound **24** (60 g) in THF (1 l.) was cooled in a Dry Ice–acetone bath and stirred with gradual addition of 1 *M* diborane in THF (1.5 l.). The resulting mixture was allowed to warm to room temperature overnight with continued stirring. It was then heated to reflux for 1 hr and cooled, and excess diborane was quenched by addition of saturated aqueous sodium sulfate solution. The mixture was partitioned between methylene chloride and dilute aqueous sodium carbonate. The combined extracts were dried and evaporated under reduced pressure to a yellow oily mixture in which compound **25** is the major component (tlc). This oil was taken up in ethanol (200 ml), treated with concentrated HCl (20 ml), scratched, and chilled overnight. The resulting precipitate of the hydrochloride of **25** was collected, washed with ethanol, and dried to give 15.0 g (24%) of colorless powder. A sample recrystallized from ethanol had mp 247–250° and ir (Nujol) 3250 and 2600 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_2O \cdot HCl$: C, 68.56; H, 7,57; N, 8.42; Cl, 10.65. Found: C, 68.34; H, 7.66; N, 8.32; Cl, 10.58.

(b) Free Base. The hydrochloride of **25** was shaken with aqueous sodium carbonate and methylene chloride. The organic layer was dried and evaporated, and the residue was crystallized from ether to give colorless crystals of the free base. An analytical sample prepared by vacuum sublimation had mp 135–139°: ir ($CHCl_3$) 3300, 2830, 2750, and 1625 cm^{-1}; nmr ($CDCl_3$) 0.9–4.3 (well resolved but complex multiplet, singlet evident at 2.35, 20 H), 7–7.6 (m, 4 H); uv (MeOH) 231 (31,600), 277 (5700), 284 (6200), and 294 mμ (5430); mass spectrum *m/e* 295 (100%) and 296 (M^+).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.13; H, 8.20; N, 9.32.

12-(β-Aminoethyl)-6,7,8,9-tetrahydro-7a,11a-ethanooxyindolo[1,2-*h*][1,7]naphthyridin-10(11*H*)-one (26). A slurry of compound **24** (10 g) and wet Raney nickel (500 mg) in glacial acetic acid was shaken under 50–60 psi of H_2 for 48 hr. The catalyst was filtered out and washed with methylene chloride. Evaporation of the filtrate under reduced pressure left a syrup which was taken up in water. The precipitate which formed gradually was filtered, washed, and air dried to give 1.7 g of recovered nitrile **24**. The filtrate was made basic with aqueous sodium carbonate and extracted three times with methylene chloride. The residue from the dried extract after evaporation was crystallized from ethanol to give 3.55 g (42%) of colorless crystals. A sample was recrystallized from ethanol for analysis giving crystals with mp 182–185°: ir (Nujol) 3300, 1665, and 1585 cm^{-1}; nmr ($CDCl_3$) 1.0–4.4 (complex but well-resolved multiplet, 18 H), 7–7.7 (m, 4 H), and 10.3 (s, broad, NH); mass spectrum *m/e* 296 (100%) and 325 (M^+).

Anal. Calcd for $C_{19}H_{25}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 69.71; H, 7.36; N, 12.68.

***d,l*-18,21-Oxidodihydroeburnamenin-3-one (27).** Compound **26** (1.3 g) was vacuum distilled slowly (overnight) in a Kugelrohr distillation apparatus using an oven temperature of 253° (0.3 mm). The product was obtained pure (tlc) as a pale yellow glass (1.2 g, 97%).

Crystallization from methanol gave colorless crystals with mp 160–163°: ir (Nujol) 1640 and 1600 cm^{-1}; nmr ($CDCl_3$) 1.6–3.1 (m, 10 H), 3.3–4.4 (m, 5 H), 4.9 (8 line m, 1 H), and 7.0–7.7 (m, 4 H); mass spectrum *m/e* 264 (100%) and 308 (M^+).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.53; N, 9.08. Found: C, 73.98; H, 6.65; N, 9.11.

14-(18-Hydroxydihydroeburnamenin-3-yl)-18-hydroxy-$\Delta^{3,14}$-dehydrodihydroeburnamenine (28). A solution of compound **27** (500 mg) in THF (10 ml) was treated with excess Red-Al in benzene (70% solution) and kept overnight at room temperature. The reaction was quenched with saturated aqueous sodium sulfate and partitioned between ether and 3 *N* HCl. The yellow acid layer was washed with ether, made basic with sodium carbonate, and extracted with methylene chloride. The major product contained in this extract was isolated by preparative tlc on silica gel plates and recrystallized from methylene chloride–ether to give 150 mg (31%) of colorless crystals with mp 265–270° dec: ir (Nujol) 3300, 1650 (w), and 1630 cm^{-1} (w); nmr ($CDCl_3$–DMSO-d_6) 1.0–4.4 (complex multiplet, 35 H), 6.15 (s, 1 H, vinyl), 7.0–7.6 (m, 8 H); mass spectrum *m/e* 294 (100%) and 588 (M^+). The compound shows a single spot on tlc although several diastereomers are possible.

Anal. Calcd for $C_{38}H_{44}N_4O_2$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.26; H, 7.58; N, 9.32.

***d,l*-18,21-Oxidodihydroeburnamenine (29). (a) From the Hydrochloride of 25.** A solution of the hydrochloride of **25** (4.5 g) in water (450 ml) was treated with the disodium salt of EDTA (22.5 g) and mercuric acetate (13.5 g). The solution was heated on the steam bath for 25 min during which it turned yellow and metallic mercury separated. The cooled solution was filtered through Celite and made strongly basic by adding sodium carbonate and then sodium hydroxide. The solid product was filtered out, washed with water, air dried, and recrystallized from methylene chloride–ether to give 3.95 g (99%) of **29** in three crops. An analytical sample was recrystallized from ether to give colorless crystals with mp 149–152°: ir (Nujol) 1600 cm^{-1} (w); uv (ref 19); nmr ($CDCl_3$) 1.2–3.3 (m, 13 H), 3.5–4.4 (m, 5 H), and 7.0–7.7 (m, 4 H); mass spectrum *m/e* 250 (100%) and 294 (M^+).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.44; H, 7.56; N, 9.50.

(b) From Compound 32. A mixture of compound **32** (12 g), 1,2-dibromoethane (60 g), and potassium carbonate (60 g) in diglyme (400 ml) was stirred and heated under reflux for 16 hr. The cooled mixture was diluted with 1 l. of water, acidified with 3 *N* HCl, and washed with ether. The aqueous layer was made basic with aqueous sodium carbonate and extracted three times with methylene chloride. The residue from this extract after drying and evaporation (boiling water bath) was taken up in 50 ml of ethanol. Scratching and seeding induced crystallization of compound **29**. After standing overnight, the first crop was filtered, washed with cold ethanol, and dried to give 6.4 g of product. Chromatography of the mother liquor on silica gel provided an additional 1.7 g of product to give a total of 8.1 g or 61%.

***d,l*-18-Hydroxydihydroeburnamenine (30).** The yellow solution obtained by dissolving compound **29** (500 mg) in glacial acetic acid (20 ml) was treated with zinc dust (5 g) in small portions with stirring. After 40 min, the mixture was diluted with water, filtered through Celite, treated with disodium EDTA (to keep zinc salts in solution), made basic with sodium hydroxide solution, and extracted three times with methylene chloride. The solid residue from the dried extract after evaporation consists of compound **30** with a small amount of the less polar trans isomer **25** present as an impurity. This was removed by a single recrystallization from ethanol giving 400 mg (80%) of pure cis alcohol **30** as colorless crystals with mp 180–182°: ir ($CHCl_3$) 3100, 1620, and 1590 cm^{-1}; nmr ($CDCl_3$) 1.0–4.4 (complex multiplet, 20 H) and 7.0–7.7 (m, 4 H); mass spectrum *m/e* 296 (100%, M^+).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.83; H, 8.16; N, 9.36.

7a-(β-Hydroxyethyl)-6,7,7a,8,9,10,11,11a-octahydroindolo[1,2-*h*][1,7]naphthyridine (31). Lithium aluminum hydride (12 g) was added gradually to a solution of compound **22** (40 g) in THF (600 ml) and the resulting mixture was stirred and heated under reflux overnight. Excess hydride was quenched by addition of saturated aqueous sodium sulfate. The precipitate was filtered off and thoroughly washed with methylene chloride and hot THF. After drying and evaporation, the residue was triturated with ether, filtered, and washed with ether giving 33.1 g (86%) of **31** in two crops of colorless crystals. An analytical sample was obtained from ether as needles with mp 215–219°: ir (Nujol) 3250, 3100, 1680 (w), and 1550 cm^{-1} (w); nmr ($CDCl_3$–DMSO-d_6) 0.8–2.3 (m, 8 H), 2.6–4.5 (m, 9 H), 6.30 (s, 1 H), and 6.9–7.6 (m, 4 H); mass spectrum *m/e* 225 (100%) and 270 (M^+).

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 74.80; H, 8.24; N, 10.22.

7a-(β-Hydroxyethyl)-6,7,7a,8,9,10-hexahydroindolo[1,2-*h*][1,7]-naphthyridine (32). A mixture of compound **31** (4 g), mercuric acetate (8 g), and disodium EDTA (16 g) in water (100 ml) was heated on the steam bath for 3 hr. An additional 1-g portion of mercuric acetate was added at half-time. The cooled solution was made basic by addition of aqueous sodium carbonate and extracted several times with methylene chloride. The residue from the dried extract after evaporation was recrystallized from methylene chloride–ethanol to give 2.9 g (73%) of compound **32** in pale yellow crystals. The analytical sample obtained by vacuum sublimation was also pale yellow with mp 170°: ir (Nujol) 3150, 1635 (s), and 1530 cm^{-1}; nmr ($CDCl_3$) 1.4–2.3 (m, 9 H), 2.3–3.3 (m, 2 H), 3.5–4.4 (m, 4 H), 6.53 (s, 1 H), 6.9–7.4 (m, 3 H), and 7.55 (m, 1 H); mass spectrum *m/e* 223, 224 (100%), and 268 (M^+).

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.95; H, 7.45; N, 10.41.

***d,l*-Dihydroeburnamenine (34).** The two steps used to convert the alcohol **30** to **34** were conducted without complete purification and characterization of the intermediate aldehyde **33** or of its hydrazone. The Fetizon reagent[26] prepared from 170 g of silver nitrate precipitate onto 150 g of Celite with 150 g of sodium carbonate was stirred with the alcohol **30** (4 g) in benzene (1.5 l.) at reflux for 4 days. The progress of the oxidation was monitored by tlc. Any water present was collected in a Dean-Stark trap. The mixture was filtered and the solid thoroughly washed three times with 1:1 benzene–ethanol. Evaporation left 3.52 g of the aldehyde **33** as a brownish oil: ir (film) 2720 and 1725 cm^{-1}; nmr ($CDCl_3$) 1.0–4.4 (complex multiplet), 7.0–7.7 (m, 4 H), and 9.97 (t, J = 2 Hz, 1 H).

The crude aldehyde was treated with 97% hydrazine (5 ml) in ethanol (50 ml) and the resulting solution boiled for 1 hr. The residue after evaporation was taken up in ethylene glycol (50 ml), potassium hydroxide (5 g) was added, and the mixture was stirred and heated under reflux for 1.5 hr. The cooled reaction mixture was partitioned between water and a 2:1 benzene–ether mixture. The organic layer was washed twice with water, dried, and evaporated to afford 2.4 g of a yellow oil. Crystallization from a small amount of ether–hexane using seed crystals from a probe experiment gave 2.1 g (55.5%) of **34** as light tan crystals. The presence of a small amount of an impurity was indicated by tlc. This was removed by purification *via* the picrate as follows. The dihydroeburnamenine in methanol (10 ml) was treated with picric acid (2 g) in methanol (20 ml) and the precipitated picrate was collected, washed, and dried to give 3.8 g. Recrystallization from methylene chloride–methanol gave 3.2 g of purified picrate which was decomposed by shaking with aqueous sodium hydroxide and methylene chloride. The organic layer was dried and evaporated. The residue was taken up in ether and filtered to remove some brown insoluble material. Evaporation of the ether left an oil which was taken up in hot hexane and decanted from traces of insoluble gum. Crystallization, again induced by seeding, afforded 1.6 g of pure dihydroeburnamenine as a very pale yellow solid. An analytical sample was recrystallized once more from ether–hexane giving colorless crystals with mp 100–104°: ir (Nujol) 1620 (w) and 1580 cm^{-1} (w); nmr ($CDCl_3$) 0.90 (t, J = 7 Hz, 3 H), 1.1–4.4 (complex multiplet with a singlet evident at 3.22, 17 H), and 7.0–7.7 (m, 4 H); mass spectrum *m/e* 280 (100%, M^+).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.33; H, 8.53; N, 9.88.

***d,l*-Epidihydroeburnamenine (36).** The oxidation of alcohol **25** (3 g) to the aldehyde **35** was effected in benzene (700 ml) using the Fetizon reagent prepared from 85 g of silver nitrate precipitated onto 75 g of Celite with 75 g of sodium carbonate. The oxidation was complete after 36 hr. The crude aldehyde, isolated as described above, had: ir (film) 2700 and 1705 cm^{-1} (s); nmr ($CDCl_3$) 1.0–4.4 (complex multiplet), 7.0–7.7 (m, 4 H), and 9.72 (t, J = 2 Hz, 1 H).

This aldehyde was treated with hydrazine hydrate (4 ml) in ethanol (45 ml) and heated on the steam bath for 1 hr. The residue after evaporation was taken up in ethylene glycol (50 ml), treated with potassium hydroxide (4 g), and stirred under reflux for 1.5 hr. Using the work-up procedure described for compound **34**, compound **36** was obtained in crude form as a yellowish solid (2.25 g). The yellow impurity was removed by filtration of a methylene chloride solution through a Florisil bed followed by recrystallization

from methylene chloride–ether. Pure epidihydroeburnamenine was thus obtained in two crops of colorless crystals (1.75 g, 62%) with mp 183–184°: ir (Nujol) 1625 cm^{-1}; nmr ($CDCl_3$) 0.76 (unsym t, 3 H),[29] 0.9–3.3 (m, 15 H), 3.5–4.3 (m, 2 H), and 7.0–7.6 (m, 4 H); mass spectrum *m/e* 279 (100%) and 280 (82%, M^+).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.21; H, 8.37; N, 9.89.

(29) Unlike the case with **34**, the ethyl group of **35** does not appear to be a simple A_3B_2 system, probably as a consequence of its more hindered environment.

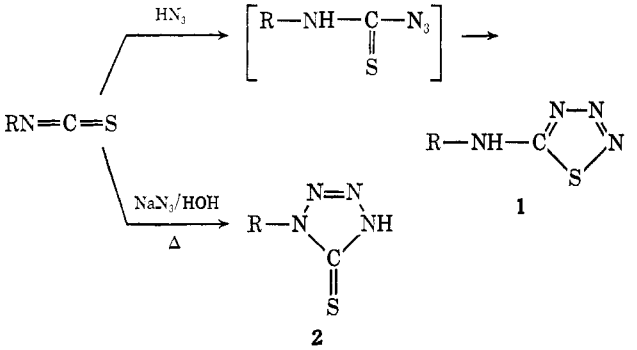
4-Alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines. Interesting Starting Materials for the Synthesis of Sulfonylcarbodiimides and Novel Heterocycles

Gerrit L'abbé,* Emiel Van Loock, Rudolf Albert, Suzanne Toppet, Gabriël Verhelst, and Georges Smets

Contribution from the Department of Chemistry, University of Louvain, Celestijnenlaan 200F, B-3030 Heverlee, Belgium. *Received January 12, 1974*

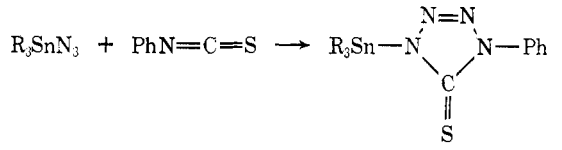
Abstract: Alkyl azides react with sulfonyl isothiocyanates at room temperature to give 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (**4**) in reasonable good yields (49–76%). These heterocyclic compounds are smoothly thermolyzed at 45–80° to sulfonylcarbodiimides **5**. When heated in the presence of enamines, 4-aminothiazolidines (*e.g.*, **11–13**) and/or thiazolines (*e.g.*, **17** and **18**) are obtained, the latter resulting from the 4-aminothiazolidines by loss of amine. Ynamines and keto-stabilized phosphorus ylides also react with the thiatriazolines to give thiazolines (*e.g.*, **20**, **22–24**), whereas vinyl ethers, vinyl acetates, and electron-poor olefins and acetylenes are unable to give addition products. Structure assignment of the new products was based on chemical evidence and spectroscopic study including ^{13}C nmr analysis. The mechanism of thiazolidine formation is discussed.

The behavior of isothiocyanates toward inorganic azides is well known.[1] Thus, the reaction of hydrazoic acid with isothiocyanates furnishes 5-(substituted) amino 1,2,3,4-thiatriazoles (**1**) probably *via* unstable thiocarbamoyl azides. Sodium azide, on the contrary, reacts with isothiocyanates to give 1-substituted-Δ^2-tetrazoline-5-thiones (**2**) which are also obtained in part by the base-catalyzed isomerization of **1** when R = aryl.



2

Recently, Dunn and Oldfield[2] reported the reaction of tri-*n*-butyltin azide and triphenyltin azide with phenyl isothiocyanate to give the C=N adducts **3**. These were converted to **2** (R = Ph) upon treatment with cold dilute HCl. Other organometallic azides also produced C=N adducts.[3]



3, R = *n*-Bu or Ph

No reactions of isothiocyanates with organic azides have thus far been reported, although reactions with other 1,3-dipoles are known:[4] diazoalkanes, nitrile ylides, and azomethine ylides yield C=S adducts, azomethine imines and nitrones give C=N adducts and nitrile imines are capable to add onto the C=N and/or C=S bonds of isothiocyanates. In view of these results, addition of azides across the C=N and/or C=S bonds of isothiocyanates may formally be considered. We have now found that alkyl azides react readily with sulfonyl isothiocyanates to give 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (**4**) exclusively.[5] Despite the large number of investigations carried out with the aromatic 1,2,3,4-thiatriazoles,[6] 1,2,3,4-thiatriazolines have only been mentioned in a few reports.[3,7]

Results and Discussion

The reaction of *n*-butyl azide and benzyl azide with equimolar amounts of sulfonyl isothiocyanates at room temperature readily afforded 4-alkyl-5-sulfonylimino-

(1) See, for instance, E. Lieber, C. N. Pillai, and R. D. Hites, *Can. J. Chem.*, **35**, 832 (1957); E. Lieber and J. Ramachandran, *ibid.*, **37**, 101 (1959), and references cited therein.
(2) P. Dunn and D. Oldfield, *Aust. J. Chem.*, **24**, 645 (1971).
(3) P. Kreutzer, C. Weis, H. Boehme, T. Kemmerich, W. Beck, C. Spencer, and R. Mason, *Z. Naturforsch. B*, **27**, 745 (1972).
(4) Review: E. Van Loock, *Ind. Chim. Belg.*, in press.
(5) For a preliminary report on this topic, see E. Van Loock, J. M. Vandensavel, G. L'abbé, and G. Smets, *J. Org. Chem.*, **38**, 2916 (1973).
(6) Review: K. A. Jensen and C. Pedersen, *Advan. Heterocycl. Chem.*, **3**, 263 (1964).
(7) E. Lieber, E. Oftedahl, and C. N. R. Rao, *J. Org. Chem.*, **28**, 194 (1963); R. Neidlein and J. Tauber, *Arch. Pharm. (Weinheim)*, **304**, 687 (1971).