54.5 (s, quat C), 53.1 (s, quat C), 50.6 (s, quat C), 30.5 (q, J_{C-H} = 132 Hz), 27.0 (q, J_{C-H} = 132 Hz), 21.2 (q, J_{C-H} = 132 Hz); IR 1730 (C=O) cm^{-1}. Exact mass calcd for $C_{10}H_{18}OS$, 186.108; found, 186.107.

Acknowledgment. We are indebted to F. Van Bolhuis of the Department of Chemical Physics of this university for carrying out the X-ray structural determinations cited in this article.

Registry No. 3a, 74966-44-2; **3b**, 74966-46-4; **6**, 4388-87-8; **7**, 83044-60-4; **9**, 83044-61-5; **10**, 6838-61-5; **11**, 74966-57-7; **12**, 74966-45-3; **14**, 83044-62-6; **15**, 83044-63-7; **16**, 83044-64-8; **17**, 83044-65-9; **18**, 83044-66-0; **19**, 83044-67-1; **20**, 73368-55-5; **21**, 83044-68-2; **23**, 83044-69-3; **24**, 83044-70-6; **29** (R = H), 83044-71-7; **29** (R = Me), 83044-72-8; **31**, 83044-73-9; **32a**, 83044-74-0; **32b**, 83044-75-1; **43**, 74966-50-0; **45**, 13905-13-0; **46**, 83044-76-2; **47**, 83044-77-3; **49**, 83044-78-4; **50**, 83044-79-5; **51**, 74966-52-2; **53**, 598-26-5; **54**, 924-50-5; **56**, 74966-53-3; **58**, 74966-51-1; **59**, 53942-65-7; **62**, 83044-80-8; **63**, 83044-81-9; ethyl isobutyrate, 97-62-1.

2-Cyano-Δ^3-piperidines. 5.[1] Toward the Synthesis of Corynanthe-Type Indole Alkaloids. Computer-Assisted Study of the Conformations of an "Inside" Indoloquinolizidine Series[2]

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1-[β-[N_a-(Phenylsulfonyl)indol-3-yl]ethyl]-2-cyano-Δ^3-piperidines **21** and **26** have been used to mimic the two-step reaction sequence **7** → **8** (Scheme I) in which a 5,6-dihydropyridinium salt, **7**, acts as a potential precursor of the tetracyclic corynanthe-type indole alkaloids. The required amino nitriles **21** and **26** were prepared by an established four-step procedure from the corresponding pyridinium salts.[10,11] Amino nitrile **21** was successfully condensed with sodium dimethyl malonate, giving the enamine **27** which in certain experiments was reacted with KCN to give the corresponding amino nitriles **32** and **34**. The benzenesulfonyl protecting group of **27**, **32**, and **34** was efficiently removed by using *t*-BuOK in THF and the C ring subsequently closed by reaction with HCl in MeOH. Three tetracyclic indoles (**29**–**31**) were obtained on cyclization of the deprotected enamine **28** (51% overall yield from **21**). In accord with this mechanism, on cyclization of deprotected amino nitrile **33**, indoles **30** and **31** were formed, and on ring closure of amino nitrile **35**, indole **29** only was formed. Because **30** and **31** were observed a priori to adopt unfavorable conformations where the malonyl and ethyl substituents were axial, a detailed analysis of the relative energies of the conformational possibilities for these products were undertaken with the aid of the computer program SCRIPT.[13] Similarly, the unsubstituted amino nitrile **26** was sequentially reacted with sodium dimethyl malonate and KCN, giving compound **37** in 75% yield. Removal of the benzenesulfonyl protecting group with *t*-BuOK in THF and cyclization by using a two-step "one pot" procedure ($AgBF_4$, HCl/MeOH) led to the formation of two tetracyclic indoles, **39** and **40**. The predominant product **40** was shown to possess the trans H-3,15 configuration typical of the alkaloid antirhine **6**.

In terms of their biogenetic origin the corynanthe-type indole alkaloids are the first of the three main families to be formed from tryptamine and secologanin.[3] Despite the considerable diversity of structural types observed within this family of alkaloids, the greater majority of these natural products display several common features,[4] i.e., an indoloquinolizidine system wherein the piperidine or D ring is further substituted at C-15 (biogenetic numbering system;[5] see **1**) by a β-dicarbonyl functionality (or modified form thereof) and at C-20 by a two-carbon unit. These features are present, for example, in the tetracyclic corynanthe alkaloids geissoschizine (**1**), corynantheine (**2**), and hirsuteine (**3**) (as well as their dihydro forms) where a formyl acetic ester unit is found at C-15 and in the pentacyclic yohimbine (**4**) and heteroyohimbine (**5**) alkaloids where the fifth or E ring has been formed by condensation of one of the carbonyl units with the appropriate fragment at C-20.

Our interest in this alkaloid series originated from the desire to develop a new, general approach toward its synthesis based upon the recognition that a similarly substituted piperidine moiety is present in each of its members.[4] An approach whereby the C-15-substituted tetracyclic system could be constructed in two steps from a 5,6-dihydropyridinium salt, **7**, is illustrated by the retrosynthetic analysis in Scheme I. The required C–C bonds would be formed by (a) condensation of a malonate anion at C-15 of the dihydropyridinium precursor **7** followed by (b) closure of the C ring. The key intermediate **8** could then be further elaborated in one of four directions, depending upon the nature of the C-20 substituents R and R′, to the yohimbine (**4**) or heteroyohimbine (**5**) systems (for which efficient methodology has been developed[6]), to

(1) For part 4 see: Harris, M.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 1511–4.

(2) This work was presented as a preliminary communication at the 2nd European Society of Chemistry (ESOC II) meeting at Stresa, Italy, June 1981.

(3) Cordell, G. A. *Llyodia* **1974**, *37*, 219–98.

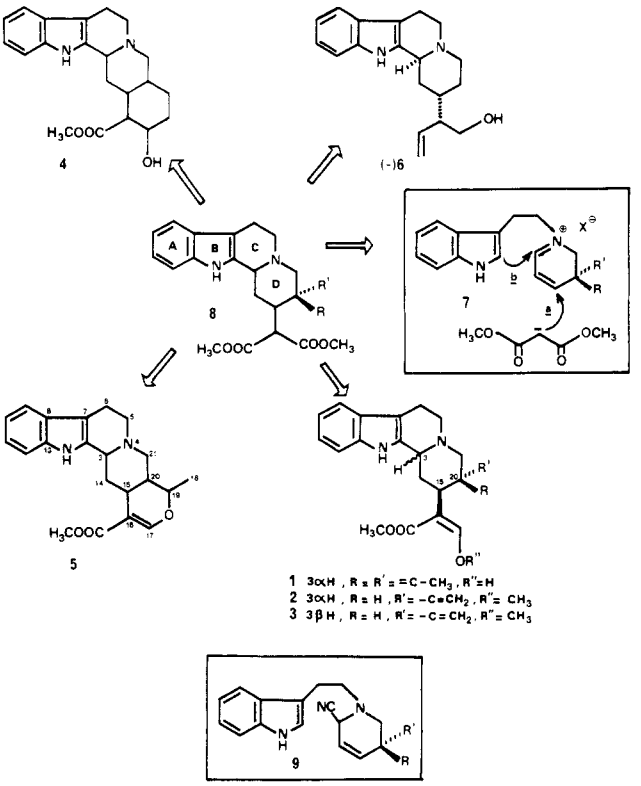
(4) Corynanthe alkaloids such as echitamine and the vobasine family do not possess the indoloquinolizidine ring system; however, their ring systems are derived from it biogenetically, and synthetic routes have been devised for rearrangement of suitable indoloquinolizidine precursors to them.

(5) Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–10. By use of this biogenetic numbering system, the α-aminonitrile carbon corresponds to C-3 since this center becomes C-3 of the tetracyclic structures.

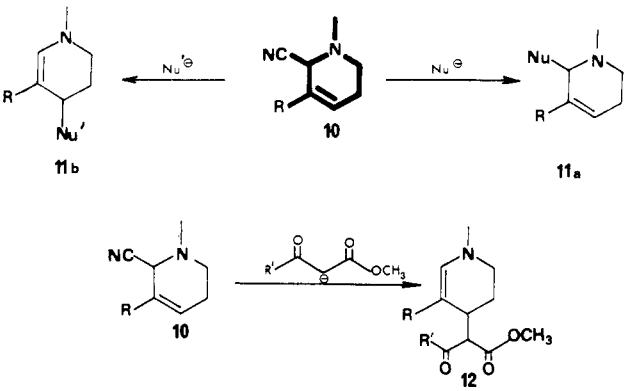
(6) (a) Wenkert, E.; Reynolds, G. D. *Synth. Commun.* **1973**, *3*, 241–3. (b) Wenkert, E. Chang, C. J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645–55. (c) Wenkert, E.; Kunesch, G.; Orito, K.; Temple, W. A.; Yadar, J. S. *Ibid.* **1979**, *101*, 4894–5. (d) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370–6. (e) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *Ibid.* **1980**, *102*, 7971–3.

0022-3263/82/1947-4439$01.25/0

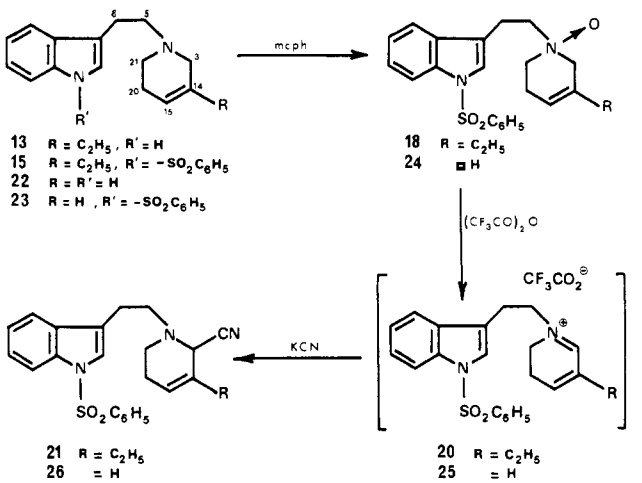
Scheme I



Scheme II



Scheme III



the alkaloid antirhine (6) by transformation of the malonyl group to a homoallylic alcohol unit,[8] or to the tetracyclic alkaloids 1–3 by partial reduction of the malonyl group.[7]

To our knowledge no reports of an approach involving such a precursor as 7 have appeared in the literature which is not surprising since 5,6-dihydropyridinium systems are known to be highly unstable. A conceptually similar route has been studied by Wenkert et al.[6] wherein enolates of malonic esters were condensed with pyridinium salts and the intermediate dihydropyridines cyclized under acid conditions to give the corynanthe system. The yields for these conversions were, however, low (≤20%), and the generality of this route was limited by the necessary stabilization of intermediate 1,4-dihydropyridines by electron-withdrawing groups at C-20. Attempts to repeat the same sequence with alkyl-substituted pyridinium salts, for instance, were unsuccessful.[6]

In recent studies we have demonstrated that 2-cyano-Δ^3-piperidines **10** represent "equivalent" forms of unstable 5,6-dihydropyridinium salts which retain the reactivity of the conjugated iminium system.[10,11] These stable allylic amino nitriles reacted regioselectively with nucleophiles at either the C-2 or C-4 positions of the piperidine nucleus, giving products **11a** or **11b** (Scheme II). In particular it was found that the reaction of amino nitrile **10** with 1,3-dicarbonyl anions led to the formation of C-4 substituted enamine products **12** in high yields.

From this result we felt that it would be possible to mimic the projected sequence **7** → **8** (Scheme I) by replacement of the unstable dihydropyridinium precursor **7** by its stable amino nitrile equivalent **9**. In this paper we report the results of our preliminary efforts to develop this route. The syntheses of two tetracyclic alkaloidal systems related to the key intermediate **8** have been achieved (Schemes III and IV). The first system prepared from amino nitrile **21** bears an ethyl side chain substituent at C-14 and is thus representative of an unnatural or "inside" series of corynanthe alkaloids.[12] The second system prepared from the unsubstituted amino nitrile **26** is a potential precursor of the natural product antirhine (**6**).

The preparation of the "inside" series was initially undertaken only as a model study since it was known from previous experience that the sensitive enamine intermediates **27** (and **28**) would be stabilized by the presence of a β-alkyl substituent.[10] However, because it was found that the products **29**, **30**, and in particular **31** adopt conformations which are a priori unfavorable, a detailed analysis of the relative energies of the conformational possibilities

(7) Dorngei, G.; Barczai-Beke, M.; Majoros, B.; Sohar, P.; Szantay, C. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 275–85.

(8) Efforts to develop a route for the conversion of the C-15 malonyl substituent to the homoallylic alcohol unit of antirhine are currently in progress in our laboratory.

(9) The formation of an unstable dihydropyridinium intermediate related to **7** has been previously demonstrated in our laboratories by its intramolecular cyclization with indole. See: Chevolot, L.; Husson, A.; Kan-Fan, C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1976**, 1222–6.

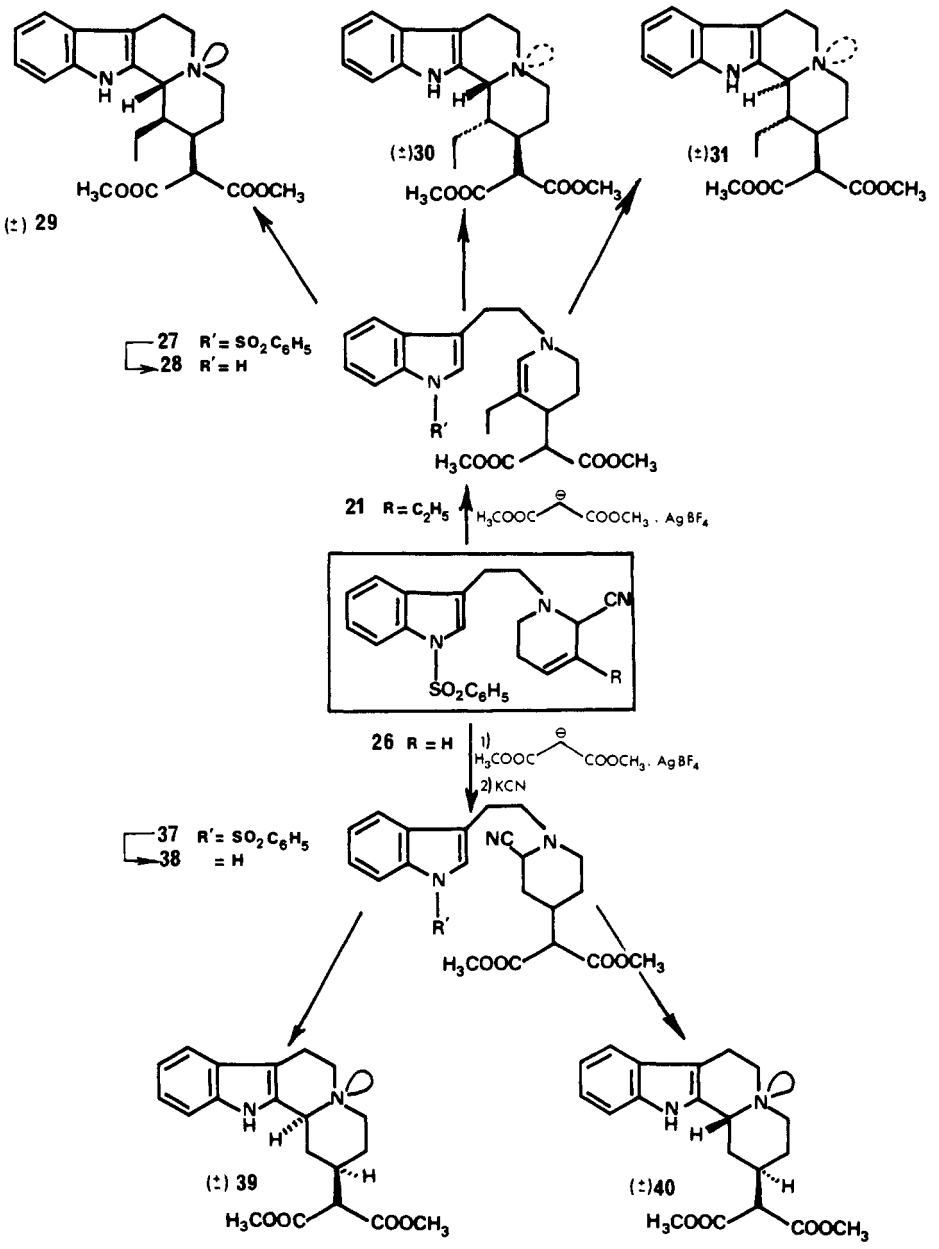
(10) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064–82.

(11) The terminology 2-cyano-Δ^3-piperidine is a precise manner to refer to a simple unsaturated piperidine α-amino nitrile system. In the present discussion where a biogenetic numbering system has been adopted and the numbering of the piperidine ring atoms thus changed it would be confusing to retain this nomenclature. Hence, compounds **21**, **26**, etc. have been referred to simply as amino nitriles **21**, **26**, etc.

(12) Morrison, G. C.; Cetenko, W. A.; Shavel, J., Jr. *J. Org. Chem.* **1967**, *32*, 2768–72. Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron*, **1973**, *29*, 2015–21.

(13) Cohen, N. C.; Colin, P.; Lemoine, G. *Tetrahedron* **1981**, *37*, 1711–21.

Scheme IV



open to these products was made with the aid of the computer program SCRIPT[13] (Schemes V and VI and Table II).

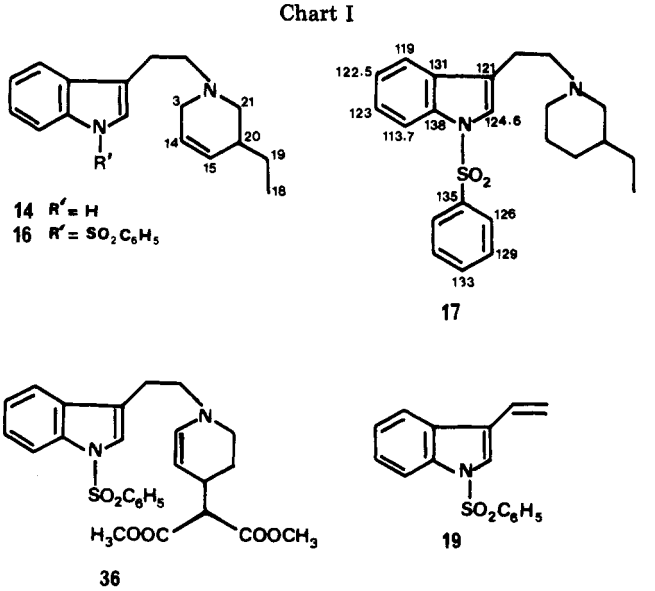
Results and Discussion

The overall synthetic sequence has been divided into two separate stages: (a) the preparation of the amino nitriles **21** and **26** (Scheme III); (b) their conversion to the two tetracyclic alkaloid systems by reaction with sodium dimethylmalonate followed by ring closure of the intermediate condensation products (Scheme IV).

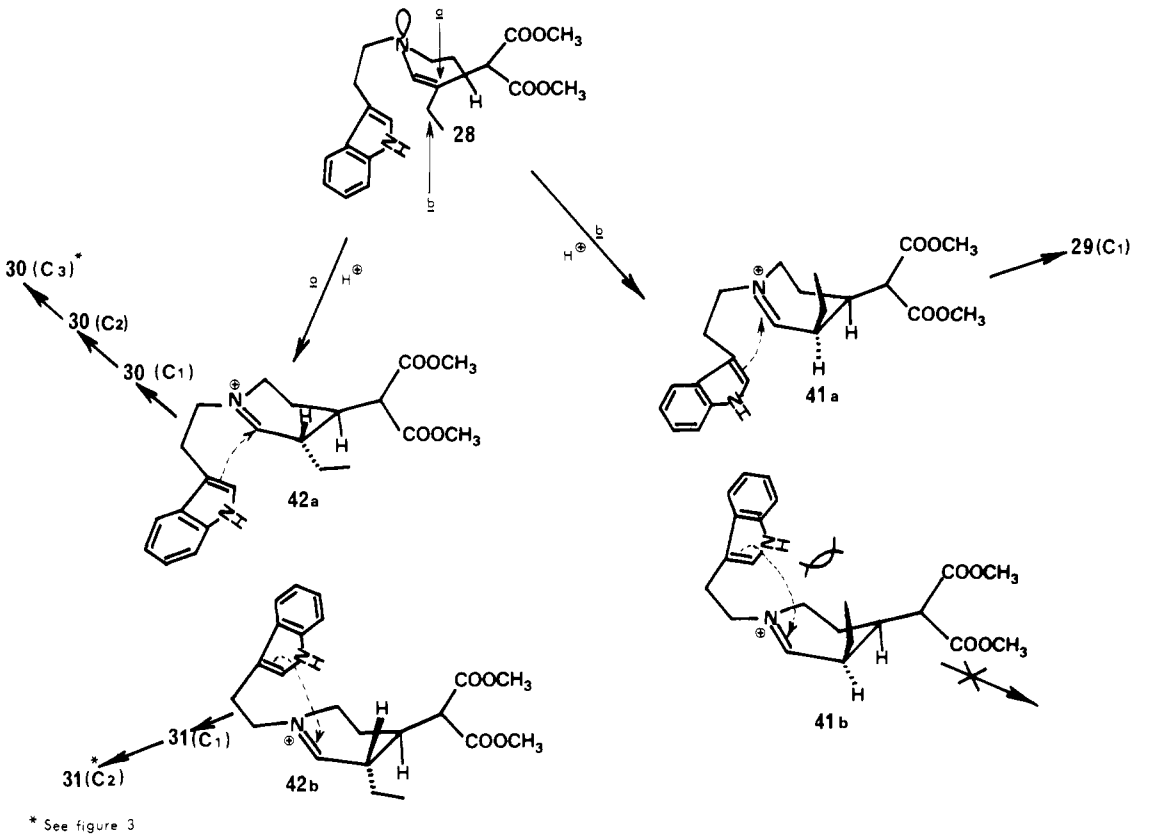
Part a has been accomplished by using experimental techniques developed in our laboratory[10] wherein 1,2,5,6-tetrahydropyridines are converted to their corresponding *N*-oxides which are in turn reacted with trifluoroacetic anhydride (Polonovski–Potier reaction), giving 5,6-dihydropyridinium salts. These unstable intermediates are immediately reacted with potassium cyanide, leading to the formation of the desired amino nitriles.

The required tetrahydropyridines **13** (obtained as a 9:1 mixture with its double bond isomer **14**, Chart I) and **22**

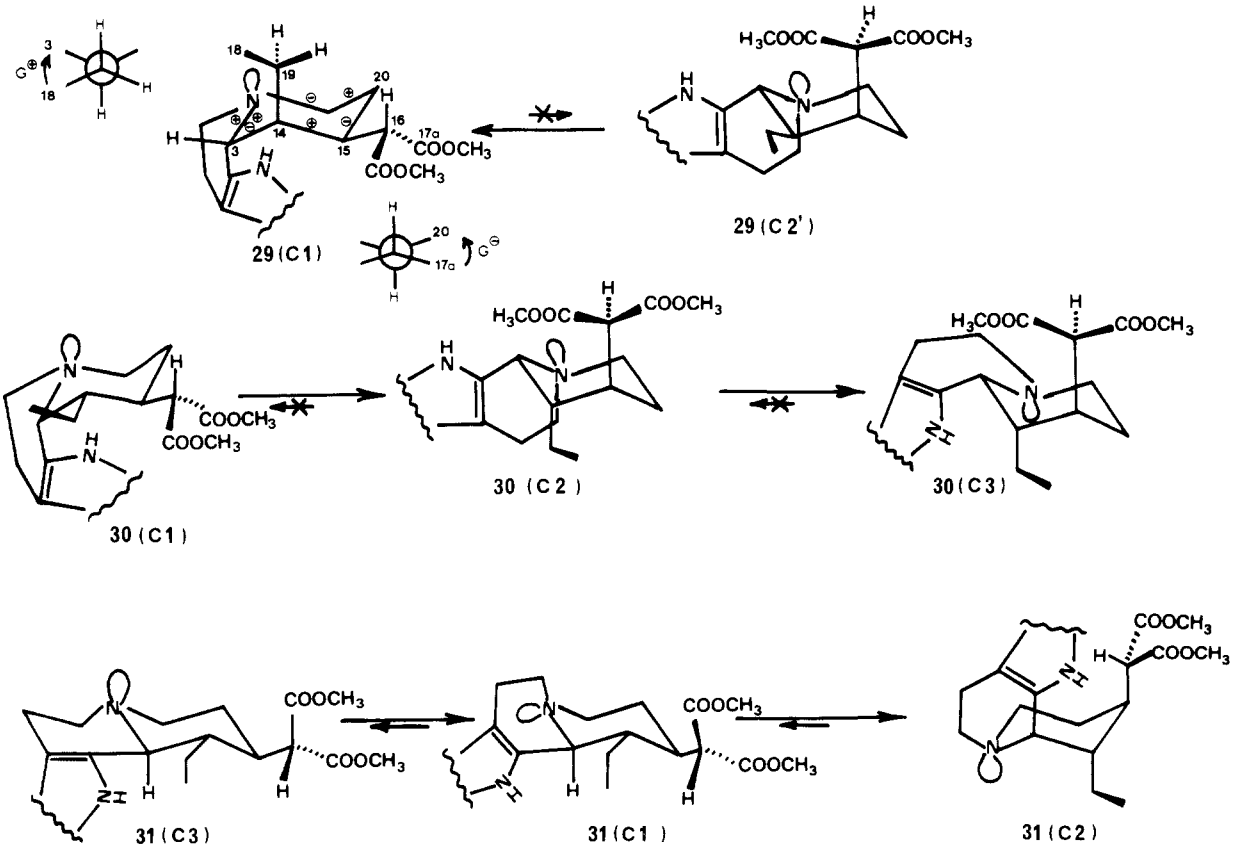
Chart I



Scheme V



Scheme VI



were prepared in 66% and 76% yields, respectively, by borohydride reduction of the corresponding pyridinium salts, which were themselves readily prepared by condensation of 3-ethylpyridine or pyridine with tryptophyl bromide according to known procedures.[14]

It was anticipated that unwanted cleavage of the C_5–C_6 bond or intramolecular cyclization could occur during re-

(14) Wenkert, E.; Massy-Westropp, R. A.; Lewis, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 3732–6.

action of the *N*-oxides of tetrahydropyridines **13** and **22** with trifluoroacetic anhydride.[15] As both these problems originate from the donating ability of the indole nitrogen lone pair, we decided to deactivate this nitrogen center by formation of the corresponding *N*-phenylsulfonyl derivatives, despite the fact that this would introduce two additional steps into the synthetic sequence. For tetrahydropyridine **13** this was efficiently accomplished by reaction of a tetrahydropyridine mixture (**13** + **14**) with benzenesulfonyl chloride under phase-transfer conditions.[16] Examination of the crude reaction mixture by TLC revealed the presence of three products which were readily separated by column chromatography on silica. The major reaction product was identified as the expected *N*-(phenylsulfonyl)tetrahydropyridine **15** (65%) and the less polar component as its isomer **16** (7%).[17] These two compounds were distinguished by the different chemical shifts observed in the ^1H and ^{13}C NMR spectra for the components of the isomeric double bonds. In the ^1H NMR spectra a broad singlet adsorption was observed at δ 5.48 for H-15 of **15** and at δ 5.71 for the olefinic protons of **16**. In the ^{13}C NMR spectra resonances were observed at δ 117.6 and 137.6 for the carbons of the alkyl-substituted double bond of **15** and at δ 124.6 and 129.9 for the carbons of the unsubstituted double bond of **16**. The chemical shifts observed for the indole and benzenesulfonyl carbons and assigned as illustrated for compound **17** were typical for the entire series of substituted indole derivatives. Also characteristic was the absorption at λ_{max} (MeOH) 250 nm in the UV spectra.

A minor more polar component identified as the saturated piperidine **17** (4%; MS, *m/e* 396; no olefinic protons in the ^1H NMR; Chart I) was presumably formed by 1,4-reduction of the pyridinium salt by borohydride in the previous step.

In an identical manner tetrahydropyridine **22** was converted to its *N*-phenylsulfonyl derivative **23** (65%) under phase-transfer conditions. Compound **23** was separated from small quantities of the fully saturated piperidine derivative by column chromatography on silica under medium pressure.

N-Oxides **18** and **24** were readily prepared by reaction of **15** and **23** with *m*-chloroperbenzoic acid in methylene chloride for 30 min at room temperature. The pure *N*-oxides (>90%) were obtained after column chromatography on silica gel. A minor nonpolar impurity (~5%) formed in each case was identified on the basis of its spectral data as the 3-vinylindole **19** (Chart I).[18]

Amino nitriles **21** and **26** were subsequently prepared by reaction of *N*-oxides **18** and **24** with tyrifluoroacetic anhydride in methylene chloride at 0 °C followed by treatment with aqueous KCN in a two-phase reaction medium. Amino nitrile **21**, a stable crystalline solid, was isolated in 52% yield after chromatographic separation from a more polar component shown to be the tetrahydropyridine **15** (Chart I). The formation of varying amounts of tetrahydropyridines was frequently observed during these reactions undoubtedly resulting from a competing disproportionation of the dihydropyridinium salts. In the ^1H NMR spectrum of **21** the resonances at δ 5.72 and 4.05 were characteristic for H-15 and H-3, respectively. It should be noted also that the signals for the bridging methylene protons (H-5 and H-6) were overlapped, giving a broad singlet at δ 2.92. Present in the ^{13}C NMR spectrum were resonances at δ 54.9, 123.2, 133.0, and 116.3 assigned to carbons 3, 14, and 15 of the piperidine ring and to the cyano group, respectively.[10]

Amino nitrile **26** was observed to be considerably less stable than **21** to chromatography on alumina. However, by rapid filtration of the crude reaction mixture through a short column of alumina more polar materials could be removed and **26** obtained in essentially pure form as a pale orange viscous oil (72%). The observation of a singlet absorption at δ 4.15 for H-3 in the ^1H NMR spectrum and peaks at δ 54.5 and 115.9 for C-3 and CN in the ^{13}C NMR spectrum both indicated the presence of an α-amino nitrile moiety. Once again there was a coalescence of the signals for H-5 and H-6, and not unexpectedly there was a small downfield shift ($\Delta\delta$ = 0.2 ppm) of the multiplet resonance for H-14 (δ 5.98) relative to its position in compound **23**.

Having completed the preparation of the two amino nitriles **21** and **26**, we then studied their condensation with sodium dimethylmalonate and subsequent cyclization of the deprotected indole intermediates (Scheme IV). These steps were first examined with amino nitrile **21** since it was felt that the β-alkyl-stabilized enamine intermediate would be more easily manipulated than that derived from **26**.

The reaction of **21** with sodium dimethylmalonate in the presence of silver tetrafluoroborate led to the formation of a single enamine product **27** isolated in 90% yield after column chromatography on silica. Compound **27**, a stable yellow oil, displayed strong absorptions in its infrared spectrum at 1660, 1740, and 1760 cm^{-1} for the enamine and two carbomethoxy systems, respectively. In the ^1H NMR spectrum a singlet absorption was observed at δ 5.75 for H-3, a doublet resonance at δ 3.53 (J = 11 Hz) for the malonyl methine hydrogen (H-16), and a multiplet resonance at δ 2.98 for H-15. In the ^{13}C NMR spectrum the signals at δ 132.5 and 109.1 were attributed to carbons 3 and 14 and the signals at δ 52.2, 52.4, 169.0, 169.8, and 55.7 to the dimethyl malonate carbons.[10]

Cyclization of intermediate **27** was not possible due to the decrease in nucleophilicity of the indole C-2 position caused by the presence of the *N*-phenylsulfonyl group. It was thus necessary to first remove this protecting group. The conditions generally employed (OH^- or $LiAlH_4$ at reflux) for its removal[19] were considered to be too severe for the relatively fragile enamine and malonly components of the molecule. Quantitative removal (TLC emamination) of this protecting group under milder conditions was achieved, however, by treating the enamine **27** with 5 equiv of freshly sublimed *t*-BuOK in dry THF at room temperature.[20] Subsequent extraction and concentration afforded **2**, in 80% crude yield. Recoveries were low when this product was purified by column chromatography. Generally, therefore, the crude product was carried through to the cyclization step without prior purification. The observation of the molecular ion at *m/e* 384 in the mass spectrum was indicative of the formation of the depro-

(15) Ahond, A.; Cave, A.; Kan-Fan, C.; Langlois, Y.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1970**, 517–8.
(16) Illi, V. O. *Synthesis* **1979**, 136.
(17) Separation of tetrahydropyridines **15** and **16** was fortunate as the amino nitrile **9** (R′ = C_2H_5) derived from **16** is the required starting material for the preparation of the natural products dihydrocorynantheine and hirsutine. However, the preparation of **16** by borohydride reduction of the 3-ethylpyridinium salt led to insufficient quantities of this material to complete the synthesis. An alternate preparation of **9** and the total synthesis of the above-mentioned alkaloids will be reported at a later date.
(18) It is known that more forcing conditions are required to prepare **19** by cope elimination of *N*-oxides similar to **18** and **24**. See: Noland, W. E.; Sundberg, R. J. *J. Org. Chem.* **1963**, *28*, 884–5. The formation of **19** under the present conditions has not been investigated; however, a Cope Type mechanism seems unlikely. A mechanism where **19** could be formed by protonation of unreacted **15** or **23** by *m*-chloroperbenzoic acid followed by base-assisted elimination has been suggested (referee's comment).
(19) Sundberg, R. J.; Russel, H. F. *J. Org. Chem.* **1973**, *38*, 3324–30.
(20) McMurry, J. *Org. React.* **1976**, *24*, 187–224.

Table I. ^{13}C NMR Chemical Shift Values (δ) for the C and D Rings[a]

product	carbon										
	2	3	5	6	7	14	15	18	19	20	21
29	132.7	56.1	45.0	16.9	108.2	35.2	38.7	13.4	18.2	24.1	51.3
30	133.7	59.3	53.5	21.6	110.6	34.0	41.6	12.7	20.9	23.8	51.6
31	133.9	57.7	50.3	19.0	108.5	36.4	38.6	11.3	19.0	24.7	46.7
40	133.1	54.1	46.5	18.2	107.8	31.8*	31.7*			29.1	51.5
39	134.3	59.5	53.1	21.8	108.4	34.0	36.2			29.9	55.1

[a] All assignments (except one) were supported by OR experiments. An asterisk refers to chemical shift values which may be interconverted. The δ values are in parts per million downfield from Me_4Si. Average δ values for the malonate carbons are as follows: C-16, 53.9; C-17$_{a,b}$, 168–170; OCH_3, 52.3 ± 0.5. See the Experimental Section for δ values for indole carbons 8–13.

tected indole, as were a signal at δ 7.98 for the NH in the ^1H NMR spectrum, the presence of an NH absorption at 3480 cm^{-1} in the infrared spectrum, and a typical indole chromophore absorption in the UV spectrum.

Cyclization of the deprotected enamine **28** was subsequently accomplished by reaction in dry methanol presaturated with hydrogen chloride. The reaction mixture was stirred at room temperature for 3 days, neutralized, and worked up. The three indole compounds **29** (48%), **30** (7%) and **31** (15%) (total yield from **21** = 51%) were isolated in pure form after column chromatography of the reaction mixture on silica gel.

The 400-MHz ^1H NMR spectrum of the major product **29** was highly resolved, permitting the ready assignment of all the D-ring protons. The downfield position for the H-3 absorption (δ 4.38) was characteristic for the cis C/D ring juncture.[21] The coupling of H-3 with H-14 was negligible ($J_{3,14}$ < 1 Hz), suggesting a diequatorial arrangement for these hydrogens and thus an axial orientation of both the C-3 indole and C-14 ethyl substituents. The coupling of H-14 with H-15 was also shown to be small by irradiation of the downfield signal (δ 1.87) for one of the nonequivalent C-19 methylene protons, whereupon the H-14 absorption (δ 2.10, br d) collapsed to a broad singlet. The C-15 malonyl group was demonstrated to be in the equatorial position by collapse of the H-15 resonance (δ 2.19, tt, $J_{15,16} = J_{15,20ax}$ = 12.5 Hz, $J_{15,14} = J_{15,20eq}$ = 3 Hz) to a triplet of triplets on irradiation of H-14 and importantly to a doublet of triplets on irradiation of H_{20ax}. On the basis of the small $J_{3,14}$ and $J_{14,15}$ coupling constants and the established equatorial position for the malonyl group it was concluded that the molecule was in fact in the *cis*-quinolizidine conformation[22] with a diaxial configuration between C-3 and C-14 (see **29** (Cl), Scheme VI).

The complete absence of Bohlmann bands in the IR spectrum and the characteristic chemical shift values[6b,23] observed for carbons 3 and 6 (δ 56.1 and 16.9, Table I) in the ^{13}C NMR spectrum were in further agreement with structure **29**. The chemical shift position for carbon 3 was slightly downfield from that observed for carbon 3 of compound **40** (δ 54.1, Table I; see also ref 6b and 23); however, a small deshielding of this carbon by the axial ethyl group was expected. In a complementary fashion a ~5-ppm shielding of C-20 was observed due to the 1,3-diaxial interaction of the C_{20}–H bond with this side chain.

For the less polar product **30** the presence of Bohlmann bands in the IR spectrum, the observation of the C-6 resonance at δ 21.6 (Table I) in the ^{13}C NMR spectrum,[6b,23] and the upfield position of the H-3 absorption (δ 3.54) in the ^1H NMR spectrum[21] were direct indications that the molecule was a *trans*-indoloquinolizidine (Scheme VI). The diaxial configuration of the two remaining substituents was determined from the ^1H NMR spectrum. The H-3 absorption appeared as a broadened singlet which was only possible if the adjacent C-14 ethyl group was axial. The occurrence of the H-20ax signal (δ 2.24) as a triplet of triplets suggested that the C-15 malonyl substituent was also axial. This was confirmed by irradiation of the H-16 resonance (δ 3.97, d, $J_{15,16}$ = 12.5 Hz) whereupon the signal for H-15 (δ 2.75, dd) collapsed to a simple broadened doublet ($J \approx 4$ Hz). It was interesting to note that the absorption for H-16 was significantly shifted downfield from its position determined for product **29**. This is probably due to 1,3-diaxial interactions of the malonyl group with H-3 and H-21ax.

In the ^{13}C NMR spectrum the position of the C-3 absorption (δ 59.3) was nearly identical with that observed for C-3 of compound **39** (δ 59.5, Table I; see also ref 6b and 23). Apparently the shielding effect produced by the 1,3-diaxial interaction between the malonyl group and the C_3–H bond cancelled the deshielding effect expected from the C-14 axial group. Carbon 20 was shielded due to the influence of the axial ethyl group as already observed for **29**. Having the C-15 malonyl group pass from the equatorial to axial position did not influence this carbon resonance to any significant extent. However, C-15 shifted markedly downfield with respect to its position in **29** since the C_{15}–H bond was no longer involved in a 1,3-diaxial interaction.

For determination of the structure of the more polar reaction component it was necessary on the basis of the spectral data to distinguish between the conformers of the two possible remaining product configurations (see Schemes V and VI and detailed discussion below).[24] From the absence of Bohlmann bands in the IR spectrum and the downfield position of the H-3 resonance (δ 3.95, d, J = 4.5 Hz)[21] in the ^1H NMR spectrum it was concluded that the molecule adopted a *cis*-quinolizidine C/D ring conformation. Once again the ^1H NMR spectrum was well resolved; however, the determination of the orientation of the C-14 ethyl side chain was complicated by the observation that for this molecule the equatorial–equatorial and equatorial–axial coupling constants were nearly identical; i.e., $J_{ee} = J_{ae}$ = 4.5 Hz. It was clear, though, from the

(21) Lounasmaa, M.; Kan, S. K. *Tetrahedron* **1980**, *36*, 1607–11.

(22) Since the *cis*- and *trans*-indoloquinolizidine forms of these corynanthe-type compounds are interconvertible by a simple nitrogen inversion, these two states are generally considered to be conformers within a given configuration. See: Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831–4.

(23) Gribble, G. W.; Nelson, R. B.; Johnson, J. L.; Levy, G. C. *J. Org. Chem.* **1975**, *40*, 3720–5.

(24) From a consideration of the mechanism, the remaining product could be formed by cyclization of either iminium **41b** or **42b** (Scheme V). On the basis of steric arguments, cyclization of **41b** was felt to be highly unlikely. If, however, this cyclization mode happened to be the more favorable, the product would undoubtedly prefer to adopt the conformation where the C/D ring juncture would be trans, the ethyl group axial, and the malonyl group equatorial (the two alternate conformations would both be higher in energy). No correlation could be made between this structure and the spectral data.

Table II. Calculation of the Relative Stabilities of Different Conformers of Products 29-31

	product																
	29			30					31								
parameter	C1	C2	C2′	C1	C2	C3	C4	C4′	C1	C1′	C2	C3	C3′	C3″	C4	C4′	C3‴
cycle C[a]	1	2	2	1	2	1	1	1	1	1	2	2	2	2	2	2	2
cycle D[b]	2	1	1	2	1	1	4	4	2	2	1	2	2	2	3	3	2
Φ (3-14-19-18)[c]	G$^+$	G$^+$	A	G$^-$	A	A	A	G$^+$	G$^+$	G$^+$	A	G$^+$	A	G$^+$	A	G$^+$	G$^-$
Φ (20-15-16-17$_a$)[c]	G$^-$	G$^-$	G$^-$	G$^-$	G$^-$	G$^-$	G$^+$	G$^-$	G$^+$	G$^-$	G$^-$	G$^+$	G$^+$	G$^-$	G$^-$	G$^-$	G$^-$
ΔE[d]	0.0	4.1	3.3	6.4	3.2	0.0	6.3	6.6	0.0	2.4	0.5	0.8	2.4	3.9	3.2	4.7	6.7
$\Delta E'$[e]	2.2					0.0			3.3		3.8	4.1					

a RING C 1 2 b RING D 1 2 3 4 c G$^+$ G$^-$ A

[d] Relative stability (kcal/mol) between conformations for a given product. [e] Relative stability (kcal/mol) with respect to the most stable conformation **30** (C3).

magnitude of the coupling constants $J_{3,14} = J_{14,15} = 4.5$ Hz that the C-14 ethyl group was not *vic* diequatorial with either the C-3 indole or C-15 malonyl groups. Further, the single resonance (δ 1.80) observed for the H-19 methylene protons suggested that the ethyl side chain was free to rotate and thus probably axial. It was possible to establish with certainty that the C-15 malonyl group was positioned axially. The H-15 absorption appeared as a symmetrical hextet at δ 2.35 (h, $J_{15,16} = 9$ Hz, $J_{15,14} = J_{15,20eq} = J_{15,20ax} = 4.5$ Hz). This was interpretted to be due to a large coupling of H-15 with H-16 and to three smaller and equivalent couplings of H-15 with the other adjacent hydrogens. This was confirmed by irradiation of the H-16 signal whereupon the H-15 resonance collapsed to a well-defined quartet ($J = 4.5$ Hz). The important result of this experiment was the demonstration of an axial–equatorial relationship between hydrogens 15 and 20ax.

It was concluded from this spectral data that it was consistent with the C-3,14,15 triaxially substituted conformer (C2) of configuration **31** (Scheme VI). For either of the two other conformational forms for this configuration[22] large (i.e., ~12 Hz) $J_{3,14}$, $J_{14,15}$, and $J_{15,20ax}$ coupling constants would have been observed.

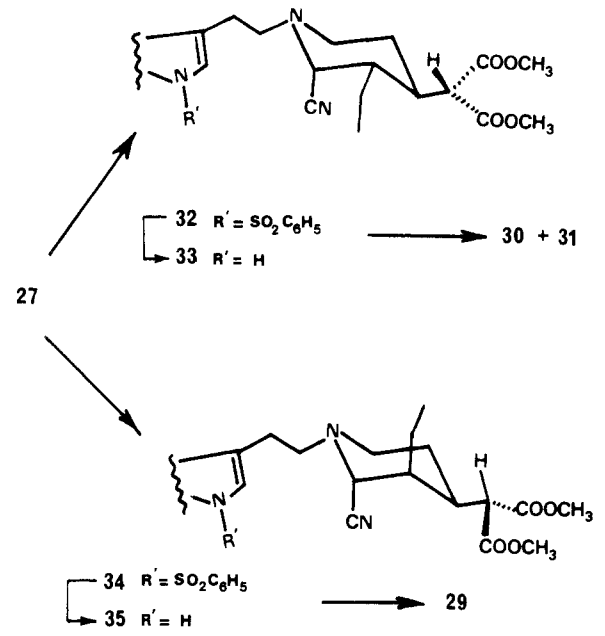
Several features of the ^{13}C NMR spectrum of this product were in agreement with the assignment of structure **31**. The carbon-15 signal (δ 38.6) was observed downfield from the corresponding signal in the spectrum of **29**. This would be expected if the malonyl group was changed from an equatorial to axial orientation. Also, the carbon 20 signals in the spectra of **29** and **31** had nearly identical chemical shifts which implied that the C-14 ethyl side chain was axial. The downfield shifts observed for the carbon 6 and 21 signals (δ 19.0, 46.7) relative to those observed for these carbons in the spectrum of **29** were unexpected however. A chemical shift of δ 19 for carbon 6 in these types of compounds has generally been taken to correspond to an equilibrium mixture between *cis*- and *trans*-quinolizidine forms.[6] As it has often been possible to detect the components of such equilibria by variable-temperature NMR experiments, the spectrum of **31** was thus recorded at both elevated and low temperatures (273 ± 70 K). At elevated temperatures only minor shifts in the peak positions were observed, and the resolution remained good. At low temperatures (>−40 °C), however, the resolution diminished rapidly, and at −70 °C additional peaks appeared in the spectrum. The resolution was too poor to enable any assignments to be made with the exception of a small peak at δ 7.83 which may correspond to a second indole NH. It is possible therefore that compound **31** exists as an equilibrium mixture of two conformers. At room temperature, however, this equilibrium appears to be highly dominated by conformer **31** (C2).

Related to the apparent anomalies in the ^{13}C NMR spectrum was the observation that the H-16 absorption in the proton spectrum was shifted markedly upfield and had a smaller coupling constant ($J_{15,16} = 9$ Hz) than that observed for this hydrogen resonance in the spectrum of **30**. In both molecules H-16 is in a sterically crowded environment, and it might be expected therefore that their chemical shifts would be similar. The perturbations observed in both the ^{13}C and ^{1}H NMR spectra could be interpreted in terms of a rotation of the malonyl group away from the H_{15}–H_{16} anti conformation so as to avoid the severe interaction with the C-3 axial indole moiety and/or in terms of a flattening of C and D rings so as to enlarge the distance between these two substituents. This latter perturbation would also explain the increase in magnitude of the equatorial coupling constant in the proton spectrum of **31**.

Mechanistic arguments for the formation of these products and a detailed discussion of their conformational preferences will be presented in a following section (Table II and Schemes V and VI).

Although the enamine **27** proved to be sufficiently stable to both chromatography and subsequent deprotection, it was felt that the same would not be true for the corresponding enamine **36** (Chart I; lacking a C-14 alkyl substituent) derived from amino nitrile **26**. For this reason a second route toward the cyclized indoles **29–31** was developed involving prior protection of the enamine function of **27** as its corresponding amino nitrile (Scheme VII). Reaction of **27** with KCN overnight in a two-phase medium buffered to pH 4.0 led to the formation of two isomeric amino nitriles **32** and **34** (4:1, 86%) which were conveniently separated by HPLC using a silica gel column. The observation of a small coupling constant ($J_{3,14} \approx 5$ Hz) for the H-3 doublet resonance at δ 3.96 and a large coupling constant ($J_{14,15} = 12$ Hz) for the H-15 triplet of triplets resonance at δ 2.10 in the ^{1}H NMR spectrum of the major isomer **32** indicated that the C-14 ethyl group was in an equatorial orientation whereas the C-3 cyano group was in the expected axial position. In the ^{1}H NMR spectrum of the minor isomer **34** the H-3 resonance (δ 3.87) appeared as a broadened singlet, implying a diaxial relationship between the cyano and ethyl substituents. The appearance of the H-15 absorption as a triplet of triplets at δ 2.67 ($J_{15,16} = J_{15,20ax} = 12.5$ Hz, $J_{15,20eq} = J_{15,14} = 2.5$ Hz) with a small $J_{15,14}$ coupling constant further indicated that the C-14 ethyl group was positioned axially. It was important to note that the H-16 resonance (δ 3.69, $J_{15,16} = 4$ Hz) of

Scheme VII



isomer **32** had a much smaller coupling constant and was significantly shifted to lower field with respect to the same hydrogen resonance in isomer **34** (δ 3.31, $J_{15,16}$ = 12.5 Hz). This signified that a rotation of the malonyl side chain in **32** had occurred in order to minimize gauche interactions with the adjacent equatorial ethyl group. As will be discussed again below, it is in part this severe interaction that the tetracyclic indoles **30** and **31** avoid by adopting an alternate conformation.

Deprotection of amino nitriles **32** and **34** with *t*-BuOK in THF proceeded without difficulty, and the two products **33** and **35** were found to be stable to chromatography on silica gel. Fortunately, the integrity of both isomers was conserved during these operations, i.e., there was no epimerization of the nitrile to the equatorial position or isomerization of the axial ethyl group of **35** to the equatorial position by reversible elimination (with enamine formation) and readdition of the cyano group in the strongly basic medium.[25] This was determined by examining the position and coupling constants for hydrogens 3 and 14–16 in the ^{1}H NMR spectrum of each isomer.

Only starting material was recovered when **33** and **35** were treated with HCl/MeOH at room temperature. When they were treated at 60–80 °C, however, the cyano group was eliminated, and cyclization did occur. In accord with the mechanism (see Scheme V), cyclization of the major isomer **33** led to the formation of the tetracyclic compounds **30** and **31**, whereas cyclization of **35** led to the exclusive formation of **29**.

Having successfully developed conditions for the elaboration of amino nitrile **21** to the "inside" compounds **29–31**, we next wanted to determine if the same set of transformations could be accomplished by using the more sensitive amino nitrile **26**.

To avoid having to isolate the unstable enamine **36**, we allowed the condensation reaction of **26** with sodium dimethylmalonate in the presence of $AgBF_4$ to proceed for approximately 20 min, and then the entire reaction mixture was poured into a two-phase medium containing an aqueous solution of KCN at pH 4.0. In this manner amino nitrile **37** was formed directly (Scheme IV). This compound proved to be relatively stable to storage under ordinary conditions; however, on chromatographic separation with silica extensive decomposition was observed. Fortunately the only major impurities were much more polar materials; hence it was possible to purify this compound by rapid passage under pressure through a short column of silica (75% yield). In the ^{1}H NMR spectrum of **37** the H-3 resonance (δ 3.93) appeared as a poorly resolved triplet, whereas a doublet (δ 3.22, J = 8 Hz) absorption was observed for H-16. In the ^{13}C NMR spectrum resonances were found at δ 52.3 and 116.1 for C-3 and the cyano group, respectively.

Despite its sensitivity to column chromatography, compound **37** was efficiently deprotected with *t*-BuOK in THF. The crude product mixture was again purified by rapid column chromatography, giving **38** in 78% yield.

It was expected that cyclization of **38** in HCl/MeOH would occur readily since attack on the iminium ion by indole was not hindered by a C-14 substituent. However, complete cyclization was not achieved even after heating for extended periods of time. Some formation of tetracyclic indoles **39** and **40** was detected, but they were present in minor quantities compared to another product (or mixture of products) which could not be properly characterized (^{1}H NMR signals for two indoles NH's, plus an unsubstituted double bond, and an absorption at 1680 cm^{-1} in the IR spectrum). Two isomeric minor products, substituted at C-3 by a methoxy group were also isolated.

Cyclization with toluenesulfonic acid in benzene at reflux gave a cleaner reaction leading to predominant formation of product **40**. Again reaction would not go to completion. The use of toluenesulfonic acid in other solvents ($CHCl_3$, dioxane, and dimethoxyethane) gave less satisfactory results.

The best results were obtained by using a two-step "one pot" procedure involving reaction of **38** with silver tetrafluoroborate in THF followed, after slow evaporation of the solvent, by treatment with HCl in methanol. In the presence of the silver salt the cyano group eliminated irreversibly, giving the corresponding enamine (isolated on several occasions) which in trail runs when the medium was evaporated to dryness underwent ring closure to the indoles **39** and **40**. Cyclization was not always complete however; hence the dry reaction mixture was generally treated with acid as a precautionary measure. By use of this method the indoloquinolizidines **39** and **40** were formed in 8% and 25% yields, respectively, from amino nitrile **38** (after chromatography).

The presence of Bohlmann bands in the IR spectrum, the upfield position of the H-3 signal (δ 3.30, br d, J = 9 Hz) in the ^{1}H NMR spectrum,[21] and the characteristic absorption at δ 21.8 in the ^{13}C NMR spectrum[23] supported the assignment of a *trans*-quinolizidine configuration for compound **39**. In a complementary manner, the absence of Bohlmann bands in the IR spectrum of **40** as well as the downfield position for the H-3 resonance (δ 4.20, br s) in the ^{1}H NMR spectrum[21] and the absorption at δ 18.2 in the ^{13}C NMR spectrum supported the assignment of a *cis*-quinolizidine configuration for this product. In both products it was determined from measurements of the coupling constants for the H-14, H-15, and H-20 absorptions in the ^{1}H NMR spectra that the malonyl substituent was in the equatorial orientation.

The predominant formation of *cis*-quinolizidine **40** (trans H-3,15 relationship) followed from earlier reports

(25) Such transformations can be achieved by using basic catalysis under the appropriate reaction conditions (unpublished observations our laboratory). Similar transformations have been reported for closely related systems: Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324–36.

on iminium cyclizations.[26,27] Although the yields of the C-20-unsubstituted tetracyclic indole system are at present only moderate, it was encouraging to find that amino nitrile **26** was stable enough to undergo reaction with the anion of dimethylmalonate and that the resulting intermediates could be manipulated. Cyclization with $AgBF_4$ was interesting in that, barring the problem of deprotection of the indole nitrogen, the condensation and ring closure reactions could be achieved in a single and potentially high-yielding operation.

We return to the discussion of the mechanism of formation of the inside tetracyclic indoles **29–31**. In principle formation of four (±) pairs of configurationally different cyclization products was possible (Scheme V), involving, first, protonation of enamine **28** from either directions a or b and, second, cyclization of iminiums **41** and **42** by approach of indole from above or below the plane of the iminium system. Cyclization via transition state **41b** was considered to be highly unlikely, however, as the approach of indole would be strongly hindered by the axial C-14 ethyl side chain which could account for the observation of only three product types in the reaction mixture.

From previous experience with enamine systems of this type[10] it has been found that under kinetic control protonation from the direction away from the face containing the malonyl group is more favorable, i.e., pathway b. This would lead to a predominant formation of indole **29** as observed [ratio of **29**/(**30** + **31**) approximately 2:1]. If the reaction were to proceed under thermodynamic control, results reminiscent of the formation of amino nitriles **32** and **34** from **27** would have been observed (Scheme VII), where a larger percentage of the C-14 equatorial ethyl side chain product **32** was formed.

The relative ratios of products **30** and **31**, formed by cyclization of iminium **42** (pathway a), were controlled by several opposing factors. The energetics of transition-state formation and steric interference by the C-15 malonyl group favored approach of indole from below the plane of the iminium ion, leading to compound **30**.[27] However, steric interactions between indole and the equatorial C-14 ethyl group would retard this mode of cyclization and lead to formation of appreciable amounts of the minor product **31**. Cyclization of the iminium **42** from either direction forcibly regenerated the nitrogen lone pair on the opposite face, leading in this case to the *cis*-quinolizidines **30** (C1) and **31** (C1) (Scheme VI). These conformations were evidently unstable, however, with respect to the alternative conformations **30** (C3) and **31** (C2) as determined from the spectral data.

Although steric interactions between adjacent D-ring substituents were released by equilibration to conformers **30** (C3) and **31** (C2), it could be seen that a number of unfavorable interactions were inherent to these conformations also.

As it was difficult on a qualitative basis to judge accurately the importance of the various factors which destabilize one conformer relative to another, we sought to obtain a quantitative estimation of the relative stabilities of the different conformational forms. With such values in hand an indication as to the position of the equilibrium between the conformers of a given configuration could be obtained, and a correlation could be made between the most stable conformation and the observed structures. To achieve this, we made use of the computer program SCRIPT.[13] SCRIPT is a conversational program which reveals the conformers and their relative energies for a given organic compound[13] (Table II, Scheme VI). With this program the exploration of the potential surface is based upon a molecular mechanics model by using a strain energy minimization criterion. Among the various factors taken into account in the determination of the molecular energy are included nonbonded and electrostatic interactions, bond stretching, bond angle bending, and torsional strain.

It is appropriate at first to make a few comments concerning the data presented in Table II. In order to describe correctly the structure, we wished to study its conformation, represented using a "conformational diagram" symbolism which gave a description of the sign of the torsion angles for each fragment of the molecule.[28] The rings C and D (indole planar) were thus represented by one of the numbered diagrams found in footnotes *a* and *b* of Table II where the plus and minus symbols represent the sign of the torsion angles. Consider as an example the conformation C1 for the *cis*-quinolizidine product **29**, formed directly on cyclization of **28**, where the conformation of the C ring is represented by diagram 1 and the D ring by diagram 2 (see Scheme VI for three-dimensional representations for each product as translated from Table II). The orientation of the ethyl and malonyl substituents are then described by determining the sign of the torsion angles Φ(3–14–19–18) and Φ(20–15–16–17a), respectively. For **29** (C1) the negative torsion angle G^- (footnote c) for Φ(20–15–16–17a) signifies that the malonyl substituent rests in the H_{15}–H_{16} anti conformation, whereas the G^+ value for the angle Φ(3–14–19–18) indicates that the C_{19}–C_{18} and C_3–C_{14} bonds are gauche to one another[29] and that the C-18 methyl group is oriented out from the D ring and away from the malonyl substituent.

Calculation of the relative energies of the two *cis*-quinolizidine conformations C1 and C2 (and C2′) for this compound showed that conformation **29** (C1) was 4.1 kcal/mol more stable than the alternate cis form **29** (C2) where the malonyl group was axial and both the indole (at C-3) and ethyl substituents were equatorial. A significant stabilization was achieved by a change in the orientation of the C-18 methyl group, **29** (C2′); however, the difference in relative stability remained large, and it was clear that there would be no tendency for the observed product **29** (C1) to equilibrate by ring inversion to conformer C2 (N inversion of conformer C1 was geometrically not possible). These calculations coincided well with the results obtained from variable-temperature NMR experiments (273 ± 70 K) which showed that the ^1H spectrum of **29** remained highly resolved even at −70 °C.

The destabilization of **29** (C2′) relative to C1 can be seen to be a consequence of a less favorable arrangement of the C-14 and C-15 substituents in C2′. From a consideration of 1,3-diaxial interactions between the C and D rings only, the conformation C2′ (two diaxial interactions) is possibly of lower energy than the conformation C1 (three diaxial interactions). However, this stabilization would be lost by the change of the malonyl group from an unhindered equatorial orientation to the axial position (two additional 1,3-diaxial interactions) and by the flip of the ethyl group into a crowded environment where its movement is largely restricted.

Looking next at configuration **30**, it was determined that

(26) Husson, H.-P.; Chevolot, L.; Langlois, Y.; Thal, C.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1972**, 930–1. Aimi, N.; Yamanaka, K.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1972**, 1081–4. See also ref 12b.

(27) Morrison, G. C.; Cetenko, W.; Shavel, J., Jr. *J. Org. Chem.* **1967**, *32*, 4089–90.

(28) Bucourt, R. *Top. Stereochem.* **1974**, *8*, 159–224.

(29) A torsion angle is considered positive if it is measured clockwise from the front substituent to the back substituent and negative when it is measured counterclockwise. See: Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521–23.

the isolated product had conformation **30** (C3). This required a ring inversion of the conformation C1 formed initially on cyclization of enamine **28** followed by a N inversion of the conformer C2 (Scheme VI). The relative energy calculations showed the following order of stabilities for **30**: C3 (0.0) > C2 (3.2) > C1 (6.4 kcal/mol). Here, even though the calculations represent an approximation of reality, the relative energy differences were found to be large, which clearly indicated that equilibration of the diequatorial conformer C1 to the observed product conformed C3 would be energetically very favorable. This result was striking in that it showed to what extent a diaxial orientation of the C-14 and C-15 substituents was more favorable than the diequatorial orientation.

The difference in relative energies between **30** (C2) and **30** (C3) could be attributed to the passage of the C_5–N bond from the axial to the equatorial position which generated the more stable *trans*-quinolizidine system and eliminated the 1,3-diaxial interaction with the C-14 ethyl group. The large calculated energy difference between C2 and C1 could be seen to be due to the interaction of the ethyl group with the C-3 indole substituent and to a very unfavorable diequatorial orientation of the ethyl and malonyl groups. A change in the orientation of the malonyl group reduced these crowding interactions, but this conformation remained higher in energy than conformation C2. Two conformations, C4 and C4′, where the D ring was twisted in order to increase the separation between substituents were also examined and found to be comparable in energy with conformation C1, and thus noncontributing.

Whereas the differences in calculated energies between the conformers of **29** and **30** were large and the calculated results were in accord with the experimental findings, for compound **31** these differences were small (0 ± 0.8 kcal/mol), and the calculations showed that the conformation **31** (C1) rather than the conformation **30** (C2) determined from the spectral data was the more stable.

In principle one might have thought that conformation C3 would be the more stable since all three groups were equatorial. However, this conformation proved to be the least stable of those studied (compare $\Delta E'$ values) as the steric interactions between the three adjacent groups was at its maximum. Once again it was found (compare C3 with C3″; ΔE = 3.1 kcal/mol) that by rotation of the malonyl group away from the H_{15}–H_{16} (G^+) anti position its interaction with the ethyl side chain was reduced [remember that the malonyl group of amino nitrile **32** was observed to adopt such a conformation (Scheme VII)]. Despite this minimization of the C-14/C-15 substituent interaction, it was still found that the C-14 ethyl group was completely restricted in its rotation. Different orientations of this side chain were examined (conformations C3, C3′, C3″), and the most favorable orientation was determined to be that where the C_3–H bond was eclipsed with the C_{19}–C_{18} ond even though this created a 1,3-diaxial-type interaction.

Conformer C1 where all three D-ring substituents were still equatorial but the ring junction was cis proved to be more stable than the *trans*-quinolizidine conformer C3 (ΔE = 0.8 kcal/mol). Although N inversion from a *trans*- to a *cis*-quinolizidine systems results in a gain in energy of ~2.6 kcal/mol,[30] it could be seen that by going from C3 to C1 the severe NH/C-14 ethyl "peri" interaction[6] would be greatly diminished. The loss of this later interaction would account for the greater stability of **31** (C1).

A comparison of conformations C1 and C2 showed again that conformer C1 was slightly more stable (ΔE = 0.5 kcal/mol). It was expected that conformation C2 would be considerably stabilized by elimination of the interaction of the C-14 ethyl group with the substituents at C-3 and C-15. It was realized, however, that in opposition to this a strong 1,3-diaxial interaction would be created between the indole and malonyl groups. This later interaction evidently appears to be the greater in energy. As described earlier, certain anomalies were noted in the spectral data for this compound which suggested that there was a deformation of the molecular framework and/or rotation of the malonyl group away from the H_{15}–H_{16} anti position. Various deformations of the C and D rings were examined by using the computer but were not found to result in an appreciable stabilization of the molecule. In contrast, rotation of the malonyl group in either direction away from the G^+ conformation resulted in a large destabilization of the molecule (>7 kcal/mol) which illustrated just how close this substituent was to the axial indole moiety.

At present we are unable to explain the contradiction between the spectral data and the calculations. It was evident that the three conformers were close in energy. The low-temperature NMR experiments indicated that product **31** exists as an equilibrium mixture, but these same data indicated that this equilibrium would be dominated by **31** (C2) and not **31** (C1). Further examination of structure **31** will thus have to be made before its assignment can be considered to be definitive.

In conclusion, preparation of the two series of tetracyclic indoles **29**–**31** and **39** and **40** in 51% and ~18% yields, respectively, from amino nitriles **21** and **26** demonstrated that by using these 5,6-dihydropyridinium equivalents it was possible to construct the C-15-substituted indoloquinolizidine nucleus of the corynanthe alkaloids by mimicking the two-step process **7** → **8** (plus deprotection) illustrated in Scheme I. The predominant formation of the product having the *trans*-H-3,15 relationship typical of antirhine was fortunate as this product represents a potential precursor of this rare natural alkaloid system.[8]

A large part of the success of this approach stems from the fact that the condensation intermediates enamine **27** (R = C_2H_5) and amino nitrile **3**, (R = H) are one oxidation state lower than the 1,4-dihydropyridine intermediates studied by Wenkert et al.[6] These compounds were found to be relatively stable and showed no tendency to revert back to starting materials, a serious complication when attempting to condense malonate anions with alkyl-substituted pyridinium salts.

At the present stage of development of this synthetic strategy there are several drawbacks which diminish the efficiency of certain steps, the most undesirable of which is the presence of a blocking group of the indole nitrogen. Its removal introduces an additional step into the synthesis at a crucial moment, necessitating isolation of intermediate reaction products which could otherwise have been carried on to the cyclization steps directly. Also, the preparation of the amino nitrile starting materials was accomplished in only moderate yields, and this route starting from the corresponding tetrahydropyridines is not amenable to the preparation of amino nitrile **9** (R = alkyl, vinyl; Scheme I) required for the synthesis of the natural series of C-20-substituted corynanthe alkaloids.

The two drawbacks are related and required the development of an entirely new and highly efficient preparation of non-N_a-protected amino nitrile starting materials.

(30) Aaron, H. S.; Ferguson, C. P. *Tetrahedron Lett.* **1968**, 6191–4.

(31) We thank Dr. S. K. Kan (Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay) for the use of his 400-MHz ^1H NMR spectrometer as well as the mass spectrometry service of the ICSN at Gif and M. Raynaud (Rhone-Poulenc SA, Vitry s/Seine, France) for the high-resolution mass spectra.

Work is currently in progress in our laboratories in this direction, and it is felt that once these products are in hand an efficient and general synthesis of the tetra- and pentacyclic corynanthe alkaloids could be realized.

Experimental Section

Infrared spectra (IR) were recorded in chloroform solution on a Perkin-Elmer 297 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimeters with polystyrene calibration. Peaks yielding structural information are reported. Ultraviolet spectra (UV) were run in methanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard, δ 0) on the IEF (Institut d'Electronique Fondamentale, Université de Paris-Sud, Orsay, France) 400-MHz spectrometer.[31] Chemical shift data are reported in parts per million downfield from tetramethylsilane, where s, d, dd, t, q, qn, h, o, and m designate singlet, doublet, doublet of doublets, triplet, quartet, quintet, hextet, octet, and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (δ, Me_4Si) on either a Bruker HX 90E (22.63 MHz) or WP 60 (15.08 MHz) instrument. High-resolution mass spectrometry was performed on an AEI MS 50 by Rhône-Poulenc Co., Vitry-sur-Seine, France,[31] and by the Mass Spectrometry Service of the ICSN at Gif. Column and thin-layer chromatography were done by using Aluminoxyd 90 or silica gel 60 (Merck, No. 9385). "Kagi" reagent (*p*-anisaldehyde/sulfuric acid/acetic acid, 1:1:98) was used to locate reaction components. Satisfactory analytical data (±0.4% for C, H, and N) have been obtained for crystalline compounds.

Borohydride Reduction of *N*-[β-(3-Indolyl)ethyl]-3-ethylpyridinium Bromide. Preparation of Tetrahydropyridines 13 and 14. The pyridinium salt (15.0 g, 45.3 mmol)[10] was dissolved in methanol (40 mL) and reacted with sodium borohydride (1.72 g, 45.3 mmol). Stirring at room temperature was continued for 1 h after the addition was completed. The reaction mixture was then diluted with water (200 mL) and extracted with methylene chloride (four times). The organic layers were washed with water and saturated brine, dried over sodium sulfate, and concentrated to give a yellow solid (~8.0 g). A major part of the unwanted impurities were precipitated by dissolving the crude reaction product in a minimum amount of ethyl acetate, and diluting with hexane (1 L). Filtration and concentration of the filtrate yielded a colorless oil which crystallized readily from benzene–hexane mixtures to give colorless crystals comprizing an approximate 9:1 mixture of tetrahydropyridines **13** and **14**, respectively: 7.6 g (66%); mp 122 °C; TLC [C_6H_6/EtOAc/Et_3N (8:1:1)]; IR 3480 cm^{-1} (NH); UV (MeOH) λ_{max} 290, 280, 272 nm; ^{1}H NMR δ 1.02 (t, J = 7.5 Hz, 3 H, H-18), 1.97 (q, 2 H, H-19), 2.20 (br s, 2 H, H-20), 2.63 (t, J = 7.5 Hz, 2 H, H-21), 2.78 (m, 2 H, H-6), 3.00 (m, 4 H, H-3, 5), 5.48 (br s, 1 H, H-15), 5.71 (br s, H-14, 15, minor isomer **14**), 7.00 (br s, 1 H, H-2), 7.12 (t), 7.19 (t), 7.35 (m), and 7.64 (d) (aromatic H), 8.18 (br s, 1 H, NH); MS, m/e (relative intensity) 254 (M^+·, 50), 124 (100).

Preparation of *N*-(Phenylsulfonyl)tetrahydropyridine Derivatives 15–17. A solution of 50% aqueous sodium hydroxide (30 mL) was added to a solution of the tetrahydropyridine mixture of **13** and **14** (7.50 g, 29.5 mmol) and tetrabutylammonium hydrogen sulfate (1.01 g, 3.0 mmol) in benzene (80 mL), and the resultant two-phase reaction mixture was stirred rapidly for 5 min at room temperature under an atmosphere of nitrogen. Benzenesulfonyl chloride (5.08 mL, 40 mmol) in benzene (40 mL) was then added dropwise over 20 min, and stirring was continued for an additional 1 h. The benzene layer was then separated and the aqueous layer washed twice with benzene. The combined benzene layers were washed with water (twice) and brine, dried over sodium sulfate, and concentrated to give a viscous brown oil. The crude product mixture (12.2 g) was purified by column chromatography on silica (500 g), eluting with ethyl acetate–methanol (2%). Middle fractions containing compound **16** contaminated with a small quantity of **15** were submitted to a second chromatography.

The less polar component corresponded to product **16**: 0.810 g (7%); IR 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 250 nm (shoulder at 280 nm); ^{1}H NMR δ 0.95 (t, J = 7.5 Hz, 3 H, H-18), 1.37 (m, 2 H, H-19), 2.12 (td, 1 H, H-21ax), 2.26 (br s, 1 H, H-20), 2.75 (m, 2 H, H-6), 2.90 (m, 4 H, H-21eq, 5,3), 3.20 (br d, 1 H, H-5 or 3), 5.71 (s, 2 H, H-15,14), 7.26 (t), 7.34 (t), 7.46 (m), 7.56 (m), 7.85 (d), and 8.0 (d) (aromatic H); ^{13}C NMR δ 11.4, 22.8, 26.7, 37.7, 52.8, 55.9, 57.6, 113.7, 119.4, 121.4, 123.0 (2 C), 124.6 (2 C), 126.5, 129.1, 129.9, 131.0, 133.5, 135.1, 138.1; MS, m/e (relative intensity), 394 (M^+·, 13), 270 (10), 253 (6), 125 (76), 124 (100); exact mass m/e 394.1716 (calcd for $C_{23}H_{26}N_2O_2S$ m/e 394.1714).

The second fraction contained the major product **15**: 7.54 g (65%); IR 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$): UV (MeOH) λ_{max} 250 nm (shoulder at 280 nm); ^{1}H NMR δ 1.02 (t, J = 7.5 Hz, 3 H, H-18), 1.98 (q, J = 7.5 Hz, 2 H, H-19), 2.21 (br s, 2 H, H-20), 2.60 (t, J = 7.5 Hz, 2 H, H-21), 2.75 (m, 2 H, H-6), 2.95 (m, 4 H, H-3,5), 5.48 (br s, 1 H, H-15), 7.45 (s, 1 H, H-2), 7.25 (t), 7.34 (t), 7.48 (t), 7.52 (m), 7.87 (d), and 8.01 (d) (aromatic H); ^{13}C NMR δ 12.2, 23.1, 26.0, 27.9, 50.2, 55.8, 57.8, 113.7, 117.6, 119.5, 121.5, 122.9 123.1, 124.7, 126.7, 129.1, 131.1, 133.6, 135.2, 137.6, 138.2; MS, m/e (relative intensity), 394 (M^+·, 5), 270 (6), 253 (3), 141 (15), 125 (75), 124 (100), 123 (75); exact mass m/e 394.1711 (calcd for $C_{23}H_{26}N_2O_2S$ m/e 394.1714).

The more polar fractions contained compound **17** (~4%): ^{1}H NMR showed absence of olefinic protons at δ ~5.60; MS, m/e (relative intensity), 396 (M^+·, 5), 283 (4), 271, 270 (5), 255 (6), 140–144 (35), 127 (80), 126 (100).

Formation of *N*-Oxide 18 and Styrene 19. *N*-Phenylsulfonyl derivative **15** (8.20 g, 20.8 mmol) was dissolved in methylene chloride (100 mL) and stirred at room temperature. *m*-Chloroperbenzoic acid (3.62 g, 21.0 mmol) was added to this solution in one portion followed immediately by the addition of a solution of sodium bicarbonate (3.0 g) in water (50 mL). The resulting two-phase reaction mixture was stirred until TLC indicated the complete disappearance of **15** (~1 h). The two layers were then separated, and the aqueous phase was extracted twice with methylene chloride. The combined methylene chloride fractions were washed with aqueous bicarbonate and brine, dried over sodium sulfate, and concentrated to give a tan foam (10.0 g). *N*-oxide **18** was obtained in pure form by filtration through a short column of silica gel, eluting with methylene chloride–methanol (6%). This compound, a colorless foam (9.19 g, 96%; homogenous by TLC), was carried directly through to the following step.

Examination of early column fractions revealed the presence of styrene **19**: 0.3 g (3%); a colorless oil; ^{1}H NMR δ 5.38, 5.83 (2 d, J = 12, 17 Hz, 1 H each, H-5), 6.77, 6.83 (dd, J = 12, 17 Hz, 1 H, H-6), 7.65 (s, 1 H, H-2), 7.30 (t), 7.37 (t), 7.45 (t), 7.55 (t), 7.78 (d), 7.92 (d), and 8.04 (d) (aromatic H); MS, m/e (relative intensity) 283 (M^+·, 100), 142 (95), 115 (100), 89 (30), 77 (65).

Preparation of Amino Nitrile 21. Trifluoroacetic anhydride (8.1 mL, 57.6 mmol), was added over 20 min to a stirred solution of *N*-oxide **18** (8.5 g, 19.2 mmol) in methylene chloride (100 mL) kept at 0 °C under an atmosphere of nitrogen. After stirring for additional 1 h an aqueous solution of potassium cyanide (5.18 g, 57.2 mmol) was added to the reaction mixture. The aqueous phase was adjusted to pH 4.0 by the addition of solid sodium acetate, and the two-phase system was stirred at room temperature for 30 min. The aqueous phase was then basified with aqueous carbonate, and the two layers were separated. The aqueous phase was extracted three times with methylene chloride. The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated to give a nearly colorless foam. The crude product was purified by column chromatography on alumina (300 g), eluting with hexane–methylene chloride (3%). Pure **21** (4.11 g, 52%) was obtained as a colorless oil which solidified under vacuum: mp 112–115 °C; IR 2220 (w, CN), 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 252 nm (shoulder at 280–290 nm); ^{1}H NMR δ 1.08 (t, J = 7.5 Hz, 3 H, H-18), 2.05 (m, 2 H, H-19), 2.20 (m, 1 H, H-20), 2.33 (m, 1 H, H-20), 2.57 (td, 1 H, H-21ax), 2.92 (apparent s + m overlapping, 5 H, H-5, 6,21eq), 4.05 (s, 1 H, H-3), 5.72 (br s, 1 H, H-15), 7.45 (s, 1 H, H-2), 7.28 (t), 7.35 (t), 7.45 (t), 7.55 (m), 7.88 (d), and 8.01 (d) (aromatic H); ^{13}C NMR δ 11.7, 23.1, 25.4, 26.6, 45.6, 54.7, 54.9, 113.7, 116.3, 119.4, 120.5, 122.5, 123.2 (2 C), 124.8, 126.7, 129.2, 130.8, 133.0, 133.7, 135.2, 138.3; MS, m/e (relative intensity) 419 (M^+·, 7), 392 (3), 294 (4), 278 (10), 260 (4), 250 (10), 151–148 with 149 (100); exact mass m/e 419.1674 (calcd for $C_{24}H_{25}N_3O_2S$ m/e 419.1666).

Preparation of Enamine 27. Silver tetrafluoroborate (1.95 g, 10.05 mmol) in dry THF (3 mL) was added via syringe to a stirred solution of amino nitrile **21** (3.25 g, 7.73 mmol) in THF (20 mL) maintained at room temperature under an atmosphere

of nitrogen. After 5 min, sodium dimethyl malonate (10.05 mmol) in THF (40 mL) was added via syringe to the solution of the silver complex (brown suspension). The resultant black reaction mixture was stirred for 1.5 h, diluted with aqueous ammonia (300 mL), and extracted with methylene chloride five times. The combined organic layers were washed three times with dilute ammonia and then with water, dried over sodium sulfate, and concentrated to give an orange viscous oil (4.0 g). Pure enamine **27** (3.65 g, 90%) was obtained as a yellow oil after purification by column chromatography on silica (ratio 30:1), eluting with ethyl acetate–hexane (7:3): IR 1760–1740 ($COOCH_3$), 1660 (enamine), 1370, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 250 nm (shoulder at 280–290 nm); ^1H NMR δ 1.02 (t, J = 7.5 Hz, 3 H, H-18), 1.87 (m, 4 H, H-19, 20), 2.85 (2 m, 4 H, H-6, 21), 2.98 (m, 1 H, H-15), 3.10 (t, J = 7.0 Hz, 2 H, H-5), 3.53 (d, J = 12 Hz, 1 H, H-16), 3.72 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 5.75 (s, 1 H, H-3), 7.37 (s, 1 H, H-2), 7.26 (t), 7.33 (t), 7.44 (t), 7.50 (m), 7.86 (d), and 8.0 (d) (aromatic H); ^{13}C NMR δ 13.5, 23.3, 25.9, 26.1, 33.8, 43.5, 52.2, 52.4, 54.8, 55.7, 109.1, 113.9, 119.5, 121.1, 123.3 (2 C), 124.9, 126.8, 129.4, 131.1, 132.5, 133.8, 135.4, 138.5, 169.0, 169.8; MS, m/e (relative intensity) 524 (M^+·, 6), 392 (20), 283–284 (10), 254, 251 (30), 229 (9), 197 (9), 143 (35), 141 (40), 124 (50), 122 (100); exact mass m/e 524.2030 (calcd for $C_{28}H_{32}N_2O_6S$ m/e 524.1980).

Preparation of 28 by Deprotection of Enamine 27. Enamine **27** (3.00 g, 5.72 mmol) was dissolved in THF (30 mL) and reacted at room temperature under an atmosphere of nitrogen with freshly sublimed potassium *tert*-butoxide (5 equiv). After 30 min the reaction mixture was diluted with brine (200 mL) and extracted five times with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to give a viscous brown oil (1.75 g, 80%) containing **28** as the largely predominating component. The crude product mixture was generally taken through to the following step without purification. A low yield of pure **28** was obtained after column chromatography on silica (ratio 30:1), eluting with ethyl acetate–methanol (4%): IR 3480, 1735, 1755 cm^{-1} (NH, $COOCH_3$); UV (MeOH) λ_{max} 290, 280, 272 nm, with large end absorption; ^1H NMR δ 0.90 (t, J = 7.5 Hz, 3 H, H-18), 1.88 (m, 4 H, H-19, 20), 2.92 (m, 5 H, H-6, 15, 21), 3.11 (t, J 7.5 Hz, 2 H, H-5), 3.49 (d, J = 12 Hz, 1 H, H-16), 3.65 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 5.75 (s, 1 H, H-3), 7.00 (s, 1 H, H-2), 7.12 (t); 7.18 (t), 7.35 (d), and 7.38 (d) (aromatic H), 7.98 (s, 1 H, NH); MS, m/e (relative intensity) 384 (M^+·, 15), 254 (63), 144 (63), 143 (35), 135 (15), 130 (35), 124 (50), 122 (100); exact mass m/e 384.2041 (calcd for $C_{22}H_{28}N_2O_4$ m/e 384.2048).

Cyclization of Enamine 28. Preparation of Indoles 29–31. The deprotected enamine **28** (1.20 g, 3.12 mmol) was dissolved in methanol (10 mL) and added via syringe to a solution of methanol saturated with hydrogen chloride (50 mL). The reaction mixture was stirred at room temperature for 3 days. It was then concentrated (water bath 30 °C) and dissolved in methylene chloride (50 mL), and the residual acid was neutralized by the addition of aqueous sodium bicarbonate. The organic layer was separated and the aqueous phase extracted three times with methylene chloride. The combined methylene chloride layers were washed with aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated to give a tan foam (1.6 g). The examination of the crude product mixture [silica, ethyl acetate–methanol (99:1)] revealed the presence of three indole products. The product mixture was separated by column chromatography on silica gel (40 g), eluting with ethyl acetate–methanol–triethylamine (97:1:1).

First Fraction. First obtained was a mixture (0.550 g) in which the principal component compound was **30**. Pure **30** (0.085 g, 7%) was obtained after a second chromatography on silica, eluting with ethyl acetate–hexane (8:2): IR 3470, 1735, 1755 (NH, $COOCH_3$), 2820–2740 cm^{-1} (Bohlmann bands); UV (MeOH) λ_{max} 282, 290 nm; ^1H NMR δ 0.90 (t, J = 7.5 Hz, 3 H, H-18), 1.25 (m, 1 H, H-19), 1.39 (br d, J = 12.5 Hz, 1 H, H-20eq), 1.55 (m, 2 H, H-19,14) 2.24 (tt, J = 4, 12.5 Hz, 1 H, H-20ax), 2.48 (td, J = 2.5, 12 Hz, 1 H, H-21ax), 2.54 (m, partly overlapped, 1 H, H-5 or H-6), 2.68 (dd, J = ~2.5, 12 Hz, 1 H, H-5 or H-6), 2.75 (dd, J = 4,12 Hz, 1 H, H-15), 2.83 (dq, J = 2.5, 12 Hz, 1 H, H-21eq), 2.93, 3.0 (2 m, 2 H, H-5 or H-6), 3.54 (br s, 1 H, H-3), 3.77 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.97 (d, J = 12.5 Hz, 1 H, H-16), 7.09 (t), 7.12 (t), 7.31 (d), and 7.46 (d) (aromatic H), 7.70 (s, 1 H, NH); ^{13}C NMR (Table I) δ 12.7, 20.9, 21.6, 23.8, 34.0, 41.6, 51.6, 52.7 (2 C), 53.5 (2 C), 59.3, 110.6, 111.0, 118.1, 119.6, 121.5, 127.6, 133.7, 134.5, 169.4 (2 C); MS, m/e (relative intensity) 384 (M^+·, 75) 383 (25), 253 (100), 223 (7), 197 (10), 184 (8); exact mass m/e 384.2045 (calcd for $C_{22}H_{28}N_2O_4$ m/e 384.2048).

Second Fraction. Compound **29** (0.574 g, 48%) was obtained as a colorless solid after drying under vacuum: IR 3470, 1735, 1755 cm^{-1}; (NH, $COOCH_3$); UV (MeOH) λ_{max} 282, 290 nm; ^1H NMR δ 1.02 (t, J = 7.5 Hz, 3 H, H-18), 1.15 (br d, J = 12.5 Hz, 1 H, H-20eq), 1.38 (m, 1 H, H-19), 1.64 (qd, J = 12.5, 4.5 Hz, 1 H, H-20 ax), 1.87 (m, 1 H, H-19), 2.10 (br d, J = 10 Hz, 1 H, H-14), 2.19 (tt, J = 12.5, 3.0 Hz, 1 H, H-15), 2.58 (dd, J = 12.5, 4.5 Hz, 1 H, H-6), 2.66 (dt, J = 11.0, 4.5 Hz, 1 H, H-21eq), 2.77 (td, J = 12.5, 3.0 Hz, H-21ax), 3.04 (m, 1 H, H-6), 3.25 (2 m, 2 H, H-5), 3.45 (d, J = 12.5 Hz, 1 H, H-16), 3.62 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.38 (br s, 1 H, H-3), 7.12 (t), 7.18 (t), 7.43 (d), and 7.50 (d) (aromatic H), 8.18 (s, 1 H, NH); ^{13}C NMR (Table I) δ 13.4, 16.9, 18.2, 24.1, 35.2, 38.7, 45.0, 51.3, 52.4, 52.6 53.9, 56.1, 108.2, 111.3, 117.7, 119.2, 121.2, 127.8, 132.7, 135.9, 168.8, 169.1; MS, m/e (relative intensity) 384 (M^+·, 42), 383 (20), 254 (40), 253 (100), 223 (15), 197 (50), 184 (30); exact mass, m/e 384.2041 (calcd for $C_{22}H_{28}N_2O_4$ m/e 384.2048).

Third Fraction. Compound **31** (0.185 g, 15%) was obtained as a pale yellow oil: IR 3460, 1730, 1750 cm^{-1} (NH, $COOCH_3$); UV (MeOH) λ_{max} 275, 282, 290 nm; ^1H NMR δ 1.07 (t, J = 7.5 Hz, 3 H, H-18), 1.65 (m, 1 H, H-20eq), 1.80 (qn, J = 7 Hz, 2 H, H-19), 1.88 (o, J = 3, 3, 9, 12 Hz, 1 H, H-20ax), 2.08 (qn, J = 4.5 Hz, 1 H, H-14), 2.35 (h, J = 4.5, 9 Hz, 1 H, H-15), 2.65 (m, 2 H, H-6,21), 2.95 (AB, partly overlapped, 2 H, H-5), 3.04 (ddd, J = 3, 9, 12 Hz, 1 H, H-21ax), 3.27 (m, 1 H, H-6), 3.44 (d, J = 9 Hz, 1 H, H-16), 3.63 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.95 (d, J = 4.5 Hz, 1 H, H-3), 7.08 (t), 7.14 (t), 7.30 (d), and 7.47 (d) (aromatic H), 8.10 (s, 1 H, NH); ^{13}C NMR (Table I) δ 11.3, 19.0, 23.2, 24.7, 36.4, 38.6, 46.7, 50.3, 52.2, 52.6, 57.7, 108.5, 110.8, 118.1, 119.4, 121.6, 127.5, 133.9, 135.8, 168.9, 170.0; MS, m/e (relative intensity) 384 (M^+·, 41), 253 (100), 197 (35), 184 (22), 170 (22); exact mass, m/e 384.2045 (calcd for $C_{22}H_{28}N_2O_4$ m/e 384.2048).

Preparation of Amino Nitriles 32 and 34 from Enamine 27. A solution of excess potassium cyanide in water was added to a solution of enamine **27** (2.06 g, 3.93 mmol) in methylene chloride (75 mL), and the resultant two-phase medium was adjusted to pH 4.0 by the addition of citric acid and stirred overnight under an argon atmosphere. The organic layer was then separated and the aqueous layer extracted three times with methylene chloride. The combined methylene chloride fractions were then washed with water, dried over sodium sulfate, and concentrated to give a yellow foam (2.0 g). The desired product was separated from minor impurities by column chromatography on silica gel (90 g), eluting with ethyl acetate–hexane (1:1). The product fractions were concentrated to give a pale yellow foam (1.93 g, 86%) which was shown by ^1H NMR to be a mixture of the two isomeric amino nitriles **32** and **34**: IR 2210 (w, CN), 1750, 1730 ($COOCH_3$), 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 255 nm (shoulder at 280–290 nm); MS, m/e (relative intensity) 551 (M^+·, 2), 524 (8), 520 (5), 393 (20), 281 (95), 254 (100).

Approximately 300 mg of the isomeric mixture was efficiently separated by preparative HPLC using a silica gel column and methylene chloride as the eluant.

Major Isomer 32: 160 mg; ^1H NMR δ 0.90 (t, J = 7.5 Hz, 3 H, H-18), 1.29 (7, 1 H, H-19), 1.73 (m, 4 H, H-19,20,14ax), 2.10 (tt, J = 4, 12 Hz, 1 H, H-15ax), 2.41 (td, J = 4, 12 Hz, 1 H, H-21ax), 2.81 (m, 4 H, H-5, 6), 2.90 (dt, J = 2.5, 12 Hz, 1 H, H-21eq), 3.69 (d, J = 4 Hz, 1 H, H-16), 3.74 (s, 6 H, OCH_3), 3.96 (d, J = 5 Hz, 1 H, H-3), 7.41 (s, H-2), 7.24 (t), 7.33 (t), 7.43 (m), 7.50 (m), 7.87 (d), and 7.98 (d) (aromatic H); ^{13}C NMR δ 10.8, 22.0, 23.0, 27.4, 38.3, 42.0, 48.7, 51.6, 52.3, 52.5, 55.3, 57.1, 113.7, 115.1, 119.4, 120.4, 123.2, 124.8, 126.7, 128.3, 129.3, 130.8, 133.7, 135.1, 138.2, 168.3, 169.1; exact mass m/e 551.2086 (calcd for $C_{29}H_{33}N_3O_6S$ m/e 551.2088).

Minor Isomer 34: 40 mg; ^1H NMR δ 0.68 (t, J = 7.5 Hz, 3 H, H-18), 1.25 (m, 1 H, H-19), 1.46 (m, 3 H, H-19,20ax,14eq), 1.78 (br d, J = ~10 Hz, 1 H, H-20eq), 2.47 (td, J = 3, 12.5 Hz, 1 H, H-21ax), 2.67 (tt, J = 2.5, 12 Hz, 1 H, H-15ax), 2.79 (m, 5 H, H-5,6,21eq), 3.31 (d, J = 12.5 Hz, 1 H, H-16), 3.73 (s, 6 H, OCH_3), 3.87 (br s, 1 H, H-3), 7.41 (s, H-2), 7.24 (t), 7.35 (t), 7.46 (m), 7.56 (m), 7.87 (d), and 7.88 (d) (aromatic H); ^{13}C NMR δ 11.8, 17.2,

22.7, 24.8, 36.1, 40.8, 48.6, 52.6 (2C), 54.3 (3C); exact mass m/e 551.2075 (calcd for $C_{29}H_{33}N_3O_6S$ m/e 551.2088).

Formation of Indole Amino Nitriles 33 and 35. The mixture of *N*-(phenylsulfonyl)indole amino nitriles **32** and **34** (1.0 g, 1.82 mmol) was dissolved in anhydrous THF (25 mL) and reacted under an argon atmosphere with potassium *tert*-butoxide (5 equiv). After 30 min the reaction was stopped by the addition of an aqueous solution of ammonium chloride (100 mL), and the aqueous phase was extracted three times with methylene chloride. The combined organic fractions were washed with water, dried over sodium sulfate, and concentrated to give a red viscous oil (crude yield 83%). Examination of the signals for the protons at H-3 and H-16 in the ^{1}H NMR spectrum of the crude product mixture showed that the amino nitrile portion of the molecule remained intact and that the relative proportion of the two isomers remained unchanged: IR 3470 (NH), 2220 (w, CN), 1750–1725 cm^{-1} ($COOCH_3$); UV (MeOH) λ_{max} 275, 285, 295 nm; MS, m/e (relative intensity) 411 (M^+·, 4), 384 (15), 281 (25), 254 (100); exact mass m/e 411.2162 (calcd for $C_{28}H_{29}N_3O_4$ m/e 411.2157).

Deprotection of Major Isomer: 32 → 33. In a separate experiment the major isomer **32** (150 mg) isolated by HPLC was deprotected as described above. The crude reaction product was purified by column chromatography on silica gel, eluting with ethyl acetate–hexane (7:3). Compound **33** was isolated as a colorless oil: ^{1}H NMR δ 0.88 (t, J = 7.5 Hz, 3 H, H-18), 1.30 (m, 1 H, H-19), 1.76 (m, 4 H, H-14ax,19,20), 2.14 (m, 1 H, H-15ax), 2.43, (m, 1 H, H-21ax), 2.85, 2.93 (2m, 4H, H-5,6), 2.98 (dt, overlapped, 1 H, H-21 eq.), 3.71 (d, J = 4 Hz, 1 H, H-16), 3.75 (s, 6 H, OCH_3), 4.05 (d, J = 4 Hz, 1 H, H-3), 7.04 (s, 1 H, H-2), 7.12 (t), 7.18 (t), 7.36 (d), and 7.61 (d) (aromatic H), 8.05 (br s, 1 H, NH); ^{13}C NMR δ 10.9, 22.0, 23.2, 27.3, 38.3, 41.8, 48.7, 51.5, 52.1, 52.4, 56.5, 56.8, 110.7, 113.1, 114.6, 118.3, 118.8, 121.2, 121.6, 126.8, 135.6, 167.7, 168.4.

Deprotection of Minor Isomer: 34 → 35. The minor isomer **34** (~40 mg) isolated by HPLC was deprotected and purified in an identical manner to that described for compound **32**. Compound **35** was obtained as a colorless oil: ^{1}H NMR δ 0.76 (t, J = 7.5 Hz, 3 H, H-18), 1.30 (m, 1 H, H-19), 1.48 (m, 2 H, H-20), 1.60 (m, 1 H, H-19), 1.78 (m, 1 H, H-14eq), 2.47 (m, 1 H, H-21ax), 2.68 (m, 1 H, H-15ax), 2.73, 2.82 (2 m, 5 H, H-5,6,21eq), 3.33 (d, J = 12.5 Hz, 1 H, H-16), 3.73 (s, 6 H, OCH_3), 3.97 (br s, 1 H, H-3), 7.01 (d, $J \approx$ 1 Hz, 1 H, H-2), 7.12 (t), 7.18 (t), 7.35 (d), and 7.58 (d) (aromatic H), 8.06 (br s, 1 H, NH); ^{13}C NMR δ 11.9, 17.2, 23.1, 24.8, 36.0, 40.6, 48.8 52.4 (2C), 54.2, 54.4, 55.9, 110.7, 113.1, 118.2, 118.8, 121.0, 121.6, 126.8, 135.6, 167.3, 167.8.

Cyclization of Indole Amino Nitriles 33 and 35. In separate experiments amino nitriles **33** and **35** were dissolved in a solution of dry methanol saturated with hydrogen chloride and treated overnight at reflux temperature. The reaction mixture was then poured into ice–water and neutralized by the addition of solid sodium bicarbonate. The desired products were extracted three times from the aqueous phase with methylene chloride. Examination of the crude reaction mixtures by TLC and the requisite column fractions after chromatography (conditions identical with those described for cyclization of enamine **28**) by ^{1}H NMR and mass spectroscopy revealed that amino nitrile **33** cyclized to give products **30** and **31** contaminated by the presence of a trace amount of **29**, whereas compound **29** was formed uniquely by cyclization of **35**.

Borohydride Reduction of *N*-[β-(3-Indolyl)ethyl]-pyridinium Bromide. Preparation of Tetrahydropyridine 22. As described for the preparation of tetrahydropyridines **13** and **14**, *N*-[β-(3-indolyl)ethyl]pyridinium bromide (17.2 g, 42 mmol) was reacted in methanol with sodium borohydride (1.59 g, 4 equiv). After an extractive workup and concentration the desired product **22** was obtained as a nearly colorless solid (7.2 g, 76%). This material was carried through to the next stage without further purification: IR 3480 cm^{-1} (NH); ^{1}H NMR δ 2.27 (m, 2 H, H-20), 2.70 (t, 2 H, H-21), 2.80 (m, 2 H, H-6), 3.03 (m, 2 H, H-5), 3.12 (m, 2 H, H-3), 5.72, 5.80 (2 m, 1 H each, H-14,15), 7.03 (d, 1 H, H-2), 7.11 (t), 7.18 (t), 7.35 (d), and 7.62 (d) (aromatic H), 8.04 (br s, 1 H, NH); MS, m/e (relative intensity), 226 (40, M^+·), 144, 143 (10), 130 (20), 125, 98 (100), 96 (50).

Preparation of *N*-(Phenylsulfonyl)indole 23. As described for the preparation of compounds **15** and **16** tetrahydropyridine **22** (7.0 g, 30.9 mmol) was reacted with benzenesulfonyl chloride (5.08 mL, 40.0 mmol) in a two-phase reaction medium (benzene/50% aqueous sodium hydroxide) with tetra-*n*-butylammonium hydrogen sulfate (1.0 g) as the phase-transfer agent. After an extractive workup the crude product mixture (10.9 g) was separated by column chromatography on silica gel (350 g), eluting at 100 mbar with ethyl acetate/methanol/triethylamine (96:2:2). Pure **23** (7.4 g, 65%) was obtained as a nearly colorless oil: IR 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 252 nm (shoulder at 280–290 nm); ^{1}H NMR δ 2.20 (m, 2 H, H-20), 2.62 (t, J = 6 Hz, 2 H, H-21), 2.70 (m, 2 H, H-6), 2.87 (m, 2 H, H-5), 3.04 (m, 1 H, H-3), 5.68, 5.77 (2 m, 1 H each, H-14,15), 7.40 (s, 1 H, H-2), 7.24 (t), 7.36 (t), 7.42 (m), 7.50 (m), 7.85 (d), and 7.97 (d) (aromatic H); ^{13}C NMR δ 22.9, 26.2, 50.0, 52.6, 57.8, 113.7, 119.4, 121.4, 122.9, 123.1, 124.6, 125.2 (2C), 126.6, 129.1, 131.0, 133.6, 135.2, 138.2; MS m/e (relative intensity) 366 (M^+·, 15), 283 (4), 270 (7), 225 (10), 141–144 (10), 129 (15), 115 (15), 96 (100); exact mass m/e 366.1414 (calcd for $C_{21}H_{22}N_2O_2S$ m/e 366.1401).

Preparation of *N*-Oxide 24. As described for the preparation of **18**, the *N*-(phenylsulfonyl)indole derivative **23** (6.0 g, 16.4 mmol) was treated in methylene chloride with *m*-chloroperbenzoic acid (3.97 g, 1.2 equiv, 85%). The crude product (8.4 g) obtained after extractive workup was purified by medium-pressure chromatography on silica gel (80 g). Highly colored less polar impurities were extracted with methylene chloride–methanol (10%), and the desired *N*-oxide **24** (isolated as a nearly colorless rigid foam; 5.7 g, 91%) was eluted with methylene chloride–methanol (20%). This compound was carried directly through to the following step.

Preparation of Amino Nitrile 26. As described for the preparation of **21**, *N*-oxide **24** (5.4 g, 14.1 mmol) was reacted for 1 h at 0 °C under an argon atmosphere with trifluoroacetic acid anhydride (5.9 mL, 3 equiv). An aqueous solution of potassium cyanide (0.92 g, 3 equiv, in 25 mL of H_2O) was then added, and the resultant two-phase system (after adjustment to pH 4.0) was stirred for an additional 30 min. After a normal extractive workup the crude product mixture was separated by rapid column chromatography on alumina (7 × 3 cm) under medium pressure (200 mbar) by using methylene chloride–hexane (1:1) as the eluant. Minimal loss of the desired product was observed if the crude product mixture was first absorbed into a thick layer of sand above the alumina bed and then quickly adsorbed onto the alumina and flushed through the column. Essentially pure **26** (3.98 g, 72%) was obtained as a pale orange viscous oil which readily formed a rigid foam under vacuum: IR 2210 (w, CN), 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 252 nm (shoulder at 280–290 nm); ^{1}H NMR δ 2.05 (dt, J = 3, 18 Hz, 1 H, H-20eq), 2.32 (m, 1 H, H-20ax), 2.59 (td, J = 4,12 Hz, 1 H, H-21ax), 2.86 (apparent s, 5 H, H-5,6,21eq), 4.15 (br s, 1 H, H-3), 5.72, 5.98 (2 m, 1 H each, H-14,15), 7.23 (t), 7.28 (t), 7.38 (m), 7.47 (m), 7.85 (d), and 7.97 (d) (aromatic H); ^{13}C NMR δ 22.9, 25.7, 45.7, 51.2, 54.5, 113.7, 115.9, 119.3, 120.4 (2C), 123.2 (3C), 124.8, 126.6, 129.2, 130.1, 130.8, 133.7, 135.1, 138.1; MS, m/e (relative intensity) 391 (M^+·, 6), 364 (3), 283 (10), 270 (4), 223 (15), 121 (100), 96 (40), 94 (30); exact mass m/e 391.1341 (calcd for $C_{22}H_{21}N_3O_2S$ 391.1353).

Preparation of Condensation Product 37. Amino nitrile **26** (1.20 g, 3.07 mmol) in dry THF (50 mL) was reacted with silver tetrafluoroborate (0.774 g, 3.98 mmol) for 5 min at room temperature under an atmosphere of argon. A THF solution of sodium dimethylmalonate (3.98 mmol) was then added to the above heterogeneous mixture, and the resultant mixture was stirred for 15 min. It was then poured into a two-phase medium [methylene chloride/aqueous KCN (excess) buffered to pH 4.0 with citric acid] which was stirred vigourously overnight. Dilute aqueous ammonia was then added and the mixture extracted four times with methylene chloride. The combined organic fractions were dried over sodium sulfate and concentrated to give dark red oil (1.59 g). The desired product **37** (1.21 g, 75%), a pale yellow foam, was obtained after filtration under medium pressure (100 mbar) by elution through a short (7 × 3 cm) column of silica gel, eluted with ethyl acetate–hexane (7:3): IR 2210 (w, CN), 1750, 1730 ($COOCH_3$), 1365, 1170 cm^{-1} ($C_6H_5SO_2NR_2$); UV (MeOH) λ_{max} 252 nm (shoulder at 280–290 nm); ^{1}H NMR δ 1.37 (qd, J = 4, 12.5 Hz, 1 H, H-20ax), 1.65 (td, J = 4, 12.5 Hz, 1 H, H-14ax), 1.73 (dq, J = 2, 12.5 Hz, 1 H, H-20eq), 1.96 (dq, J = 12.5 Hz, 1 H, H-14eq), 2.42 (m + td, overlapped, J = ~2.5, 12.5 Hz, 2H, H-15ax,21ax), 2.78 (m, 4 H, H-5,6), 2.88 (dt, J = 12.5 Hz, 1 H, H-21eq), 3.22 (d, J = 8 Hz, 1 H, H-16), 3.73 (s, 6 H, OCH_3), 3.93

(t, J = ~2 Hz, 1 H, H-3), 7.37 (s, 1 H, H-2), 7.24 (t), 7.31 (t), 7.42 (m), 7.50 (m), 7.85 (d), and 7.98 (d) (aromatic H); ^{13}C NMR δ 22.8, 29.1, 32.4 (2C), 48.5, 52.3, (3C), 54.9, 56.3, 113.7, 116.1, 119.4, 120.5, 123.1 (2C), 124.8, 126.7, 129.7, 129.3, 130.8, 133.8, 135.1, 138.1, 168.2 (2C); MS, m/e (relative intensity) 523 ($M^{+\cdot}$, 3), 496 (25), 382 (10), 365 (35), 284 (15), 253 (75), 226 (100), 95 (70), 94 (30); exact mass m/e 523.1776 (calcd for $C_{27}H_{29}N_3O_6S$ m/e 523.1776).

Preparation of Indole 38 by Deprotection of 37. As described for the deprotection of **27**, the *N*-phenylsulfonyl amino nitrile **37** (1.2 g, 2.29 mmol) was reacted in THF with a fivefold excess of potassium *tert*-butoxide (argon atmosphere). After 30 min a saturated solution of ammonium chloride was added, and the mixture was extracted three times with methylene chloride. The combined organic fractions were dried over sodium sulfate and concentrated to give a viscous red brown oil. The crude product mixture was separated by medium-pressure chromatography on silica gel (20 g), eluting with ethyl acetate. Essentially pure **38** (640 mg, 78%) was obtained as a viscous yellow oil: IR 3480 (NH), 2220 (w, CN), 1750–1720 cm^{-1} ($COOCH_3$); UV (MeOH) λ_{max} 275, 283, 290 nm; ^{1}H NMR δ 1.43 (qd, J = 4, 12.5 Hz, 1 H, H-20ax), 1.73 (td, overlapped, J = 4, 12.5 Hz, 1 H, H-14ax), 1.77 (dq overlapped, 1 H, H-20eq), 2.00 (dq, J = 2, 12.5 Hz, 1 H, H-14eq), 2.45 (m + td, J = 3, 12.5 Hz, 2 H, H-15ax,21ax), 2.82, 2.93 (2 m, 4 H, H-5,6), 2.98 (dt overlapped, J = ~2 Hz, 1 H, H-21eq), 3.25 (d, J = 8 Hz, 1 H, H-16), 3.75 (s, 6 H, OCH_3), 4.04 (t, J = ~2 Hz, 1 H, H-3), 7.04, (d, J = ~1 Hz, 1 H, H-2), 7.12 (t), 7.20 (t), 7.35 (d), and 7.59 (d) (aromatic H), 8.02 (br s, 1 H, NH); ^{13}C NMR δ 23.1, 29.0, 32.2, 32.5 (2C), 48.6, 52.3, 52.5 (3C), 56.3, 111.2, 113.0, 116.1, 118.5, 119.1, 121.8, 127.2, 136.1, 168.2 (2C); MS, m/e (relative intensity) 383 ($M^{+\cdot}$, 5), 356 (20), 226 (100), 147 (20), 95 (15), 94 (15); exact mass m/e 383.1875 (calcd for $C_{21}H_{25}N_3O_4$ m/e 383.1844).

Cyclization of 38. Preparation of Indoles 39 and 40. Silver tetrafluoroborate (0.175 g, 0.9 mmol) in dry THF (2 mL) was added via syringe to a solution of deprotected amino nitrile **38** (0.320 g, 0.818 mmol) in THF (10 mL). The reaction mixture was stirred under a steady stream of argon for 6 h by which time the THF had completely evaporated. A saturated solution of HCl in methanol (15 mL) was then added, and stirring under an argon atmosphere at 60–80 °C was continued overnight. The reaction mixture was then poured into ice–water, neutralized with sodium bicarbonate, and extracted three times with methylene chloride. The methylene chloride fractions were dried over sodium sulfate and concentrated to give a deep orange oil. The crude product mixture was separated by column chromatography on silica gel (7 g). Compound **39** was eluted with ethyl acetate/methanol/triethylamine (98:1.5:0.5) and compound **40** with a mixture of the same solvents (95:4:1).

Pure **39** (0.024 g, 8%) was obtained as a pale yellow oil: IR 3470 (NH), 2850–2750 (Bohlmann bands), 1750–1725 cm^{-1} ($CO-OCH_3$); UV (MeOH) λ_{max} 290, 285, 275 nm; ^{1}H NMR δ 1.39 (q, J = 12 Hz, 1 H, H-14ax), 1.60 (qd, J = 4.0, 12 Hz, 1 H, H-20ax), 1.75 (dt, J = 12 Hz, 1 H, H-20eq), 2.22 (br d, J = 12 Hz, 1 H, H-14eq), 2.37 (m, 1 H, H-15ax), 2.46 (td, J = 2.5, 12 Hz, 1 H, H-21ax), 2.61 (td, J = 4, 12 Hz, 1 H, H-5), 2.72 (br d, J = 12 Hz, 1 H, H-5), 2.93 (m, 1 H, H-6), 3.05 (m, 2 H, H-6,21eq), 3.27 (d, J = 9 Hz, 1 H, H-16), 3.30 (br d, J = ~9 Hz, 1 H, H-3), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 7.08 (t), 7.13 (t), 7.30 (d), and 7.42 (d) (aromatic H), 7.81 (s, 1 H, NH); ^{13}C NMR (Table I) δ 21.8, 29.9, 34.0, 36.2, 52.7 (2C), 53.1, 55.1, 57.2, 59.5, 108.4, 110.9, 118.2, 119.5, 121.5, 127.4, 134.3, 136.1, 168.9 (2C); MS, m/e (relative intensity) 356 (100, $M^{+\cdot}$), 355 (98), 225 (90), 223 (40), 197 (20), 184 (10), 169 (10), 156 (10); exact mass m/e 356.1749 (calcd for $C_{20}H_{24}N_2O_4$ m/e 356.1735).

Pure **40** (0.073 g, 25%) was also obtained as a pale yellow oil: IR 3470 (NH), 1750–1725 ($COOCH_3$); UV (MeOH) λ_{max} 290, 285, 275 nm; ^{1}H NMR δ 1.51 (m, 1 H, H-20ax), 1.69 (m, 1 H, H-20eq), 1.78 (td, J = 4.5, 12 Hz, 1 H, H-14ax), 2.16 (m, 1 H, H-15), 2.25 (br d, J = 12 Hz, 1 H, H-14eq), 2.65 (m, 2 H, H-21eq, H-5 or H-6), 2.78 (m, 1 H, H-21ax), 3.00, 3.10, 3.21 (3 m, 3 H, H-5,H-6), 3.40 (d, J = 10 Hz, 1 H, H-16), 3.70 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.20 (hump, 1 H, H-3), 7.11 (t), 7.15 (t), 7.38 (d), and 7.48 (d) (aromatic H), 8.12 (s, 1 H, NH); ^{13}C NMR (Table I) δ 18.2, 29.1, 31.7, 31.8, 46.5, 51.5, 52.6 (2C), 54.1, 55.3, 107.8, 111.2, 117.9, 119.3, 121.4, 127.5, 133.1, 136.0, 168.8, 169.1; MS, m/e (relative intensity) 356 (100%, $M^{+\cdot}$), 355 (95), 341 (10), 325 (15), 297 (10), 241 (8), 225 (85), 223 (20), 197 (20), 184 (15), 179 (15), 156 (12); exact mass m/e 356.1731 (calcd for $C_{20}H_{24}N_2O_4$ m/e 356.1735).

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Electrochemical Reduction of Di-Schiff Bases. Synthesis of Piperazines, Indoloindoles, Diazepines, and Diazocines

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The electrochemical reduction of a series of di-Schiff bases has led to examples where products representing reduction, cyclization, and transannular cyclization are found. Useful synthetic pathways for piperazines, indoloindoles, diazepines, and diazocines are described.

Introduction

Most reports pertaining to the electrochemical reduction of Schiff bases have dealt with polarography in aqueous systems, and only infrequently with product analysis and/or nonaqueous systems. Almost no electrosynthetic studies on di-Schiff bases exist. Some azines have been examined in methanol–water mixtures by Bezuglyi et al.[1] The product obtained from two successive two-electron reduction steps was a substituted hydrazine. Lund[2] supported this work by isolating benzaldehyde benzylhydrazone on reduction of dibenzalazine in alkaline solution. Two groups, Bezuglyi et al.[3] and Scott and Jura,[4]

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