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IMIDAZOLE ALKALOIDS OF *MACRORUNGIA LONGISTROBUS*

REVISED STRUCTURES AND TOTAL SYNTHESES†

M. A. WUONOLA and R. B. WOODWARD*
Converse Memorial Laboratory, Department of Chemistry, Harvard University, Cambridge, MA 02138

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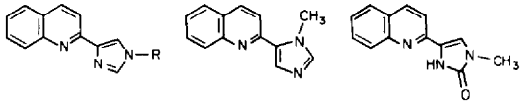
Abstract—By total synthesis, it was shown that the imidazole alkaloids dehydroisolongistrobine and isolongistrobine possess structures **1** and **2**, respectively, rather than the structures proposed by Arndt, Eggers and Jordaan in 1969. Reaction of methyl 1-methylimidazole-5-carboxylate with phenylsulfonylmethyl magnesium bromide provided a β-ketosulfone which was alkylated with *o*-nitrobenzyl bromide to provide **6**. In the key step, amino alcohol **10** and tetrahydroquinoline **8** were obtained through aluminum amalgam reduction of **6**. **8** was converted to isomacrorine **12**. **10** could be converted to **1** by a three-step sequence; **2** was obtained from **10** by acylation with 4-pentenoyl chloride, oxidation, and osmium tetroxide catalyzed periodate cleavage of the vinyl group. Comparison of samples of synthetic alkaloids **1** and **2** with the corresponding alkaloids from natural sources showed that the natural and synthetic samples of each were identical.

It has been known since before 1900 that imidazoles occur widely in nature and exhibit biological activity.[1] Most of the natural imidazoles are derivatives of histidine and histamine; other natural imidazoles include the pilocarpine alkaloids and a few other assorted alkaloids. Imidazole itself was synthesized from glyoxal and ammonia by Debus in 1858. It is not surprising, then, that by the time imidazoles were found in nature the chemistry of the system was well enough understood (largely through the researches of Pyman) that total syntheses were promptly forthcoming.

In 1964, a source of imidazole alkaloids was found to be a shrub, *Macrorungia longistrobus*, of the family Acanthaceae, indigenous to the Republic of South Africa. Arndt, Jordaan, and Joynt reported the isolation of macrorine, isomacrorine, and macrorungine from that

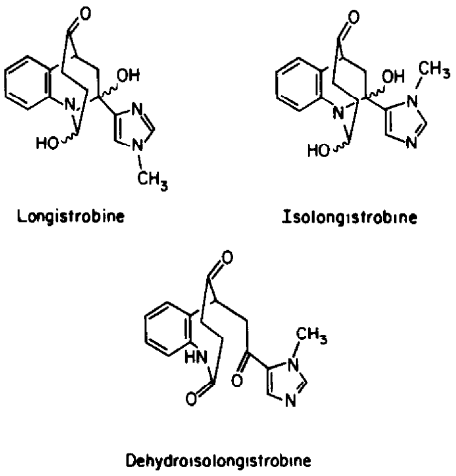


Normacrorine (R=H) Isomacrorine (12) Macrorungine
Macrorine (R=CH_3) (13)

shrub in 1964.[2] Their structures were based on a great number of degradative experiments. In 1965 the same workers reported[3] the isolation of normacrorine and the synthesis of normacrorine, isomacrorine, and macrorine from 2-acetylquinoline. The synthetic scheme proceeded in low yield but left no doubt as to the structures of these (2-quinolyl)imidazole alkaloids. "Pharmacological activity" has been attributed to isomacrorine.[4]

In 1969 Arndt, Eggers, and Jordaan reported the isolation of three more alkaloids from *Macrorungia longistrobus*: longistrobine, isolongistrobine, and dehydroisolongistrobine. These compounds were assigned tetrahydroquinoline-type structures, and the first two were formulated as dicarbinolamines.[5] One might expect that such a compound could readily aromatize (and thus not likely be isolated from a plant) by opening of the eight-membered carbinolamine, loss of water, and oxidation of the resultant dihydroaromatic system. The relationship between longistrobine and macrorine was established by zinc dust distillation, which provided the latter from the former. Isolongistrobine was converted to dehydroisolongistrobine when treated with Jones' reagent. Molecular formulae were supported by elemental analyses and exact mass measurements. However, these alkaloids exhibited *no optical activity*.

Proposed by Arndt, Eggers, and Jordaan (1969)



Longistrobine Isolongistrobine

Dehydroisolongistrobine

The spectral data concerning dehydroisolongistrobine were particularly unsettling. The nuclear magnetic resonance spectrum of dehydroisolongistrobine showed an N-methyl group (δ3.86), two imidazole protons (7.51 and 7.72), and four aromatic protons (7.0–7.3). The remaining eight protons appeared as a multiplet around δ2.9. The NH of the lactam structure proposed for dehydroisolongistrobine was not visible in the NMR spectrum.‡ Furthermore, "the infrared spectrum showed no absorption maxima in the region 3100–4000 cm^{-1} (OH and NH), but carbonyl absorption was present at ν_{max} 1710 cm^{-1}"!

The IR spectrum of dehydroisolongistrobine, if it possess the structure of Arndt *et al.*, should have IR bands not only at 1710 cm^{-1}, but also at 1670 (imidazolyl ketone[4]) and 1680–1655 (secondary amide[7]). We reasoned that these bands, had they prominently appeared, would have been reported in support of the proposed structure. It

†Based on M. A. Wuonola, Ph.D. Thesis, Harvard University (1973).

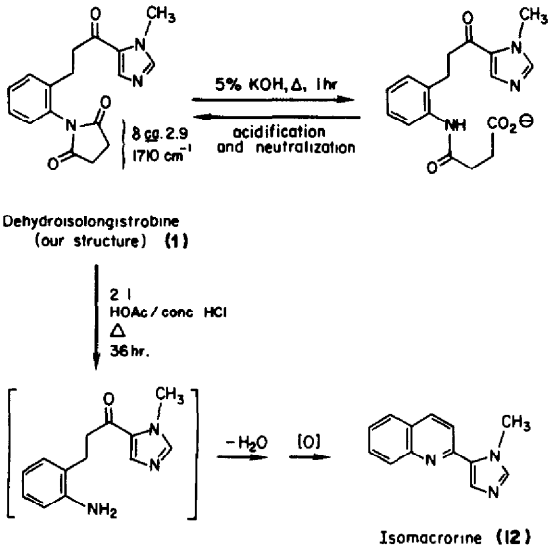
‡Such an NH would be expected to occur at about δ8 in the NMR spectrum.[6]

seemed to us that a substituted N-phenylsuccinimide structure would account for the compound's spectral properties. Several other such succinimides have IR bands near 1710 cm^{-1}[8,9] (a high-energy band at about 1780 cm^{-1} is much lower in intensity[10]). Since the succinimide band represents two carbonyl groups, it could dwarf the imidazolyl ketone band expected at 1670 cm^{-1}. In addition, the chemical shifts of typical succinimide protons[9,11] are close to that of the center of dehydroisolongistrobine's aliphatic multiplet. Our structure 1 for dehydroisolongistrobine also dispenses with the lactam, the NH of which putative moiety does not manifest itself in the spectra of the alkaloid.

Two further pieces of evidence accumulated by Arndt *et al.* support our proposal. Acid hydrolysis of dehydroisolongistrobine provided isomacrorine and succinic acid, while base hydrolysis gave a salt which on acidification and neutralization regenerated dehydroisolongistrobine. We believe that salt to be the amidocarboxylate derived from hydrolytic opening of the succinimide ring. The results of the acid hydrolysis, as well, are readily explained by our structure 1 (Scheme 1) while Arndt's structure required an elaborate and rather unreasonable mechanism.[5]

Further evidence for our hypothesis comes from the conversion of longistrobine to dehydrolongistrobine with Jones' reagent. Dehydrolongistrobine's IR and nuclear magnetic resonance spectra are qualitatively similar to those of dehydroisolongistrobine, and we can therefore formulate an imide structure for dehydrolongistrobine, as well.

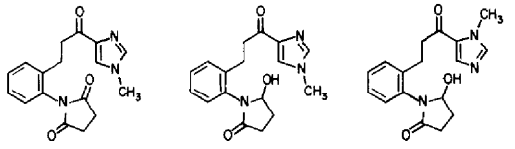
In order to discuss the structures proposed for longistrobine and isolongistrobine, it is useful to compare some UV data, presented in Table 1. The similarities among the spectra tabulated indicate that the acylimidazole chromophore is common to all the compounds. (The imidazole ring, when not conjugated with a carbonyl group, has only a weak UV absorption.) The near identity of the UV spectra tabulated is readily accounted for by postulating *dihydro* succinimide structures for longistrobine and isolongistrobine. These formulations allow for the ready rationalization of the Jones oxidations, and are consistent with the other spectral data presented by the South Africans.



Scheme I.

Table 1. UV spectra[5]

Compound	λ_{max} (ε)	λ_{max} (ε); Acid
1-Methyl-5-acetylimidazole[4]	255 (14,950)	235 (12,250)
Dehydrolongistrobine	255 (12,600)	236 (15,200)
Dehydroisolongistrobine (1)	258 (17,350)	235 (14,350)
Longistrobine	257 (11,300)	235 (14,900)
Isolongistrobine (2)	253 (16,750)	235 (14,400)



Dehydrolongistrobine (our structure) | Longistrobine (our structure) | Isolongistrobine (our structure) (2)

Our structures for longistrobine and isolongistrobine suffer from mass spectral data presented by Arndt *et al.* It is claimed that upon equilibration with deuterium oxide and monodeuteromethanol in the inlet of a mass spectrometer two hydrogens are exchanged. Since the mass spectra are complicated by ions involving proton transfer to the imidazole ring, we chose to place the mass spectral labeling data in question. Other mass spectral data were obtained after treatment of isolongistrobine with sodium in monodeuteromethanol. Such treatment could have involved reduction of the carbonyl group alpha to the imidazole ring. This could also have led to overestimation of the number of base-exchangeable hydrogens. (Our structure 2 allowed ready interpretation of the published mass spectrum[5] of isolongistrobine.)

It is also interesting to note that an anhydro product can be prepared from isolongistrobine in concentrated hydrochloric acid–acetic acid. This new material, called anhydroisolongistrobine, which differs from isolongistrobine by *one molecule* of water, could not be demonstrated to contain *any* exchangeable protons by mass spectrometry. Nor did its NMR spectrum change on addition of deuterium oxide. On the basis of the data presented by Arndt *et al.* we can formulate possible structures for anhydroisolongistrobine and an isomer (obtained from isolongistrobine in dimethyl sulfoxide) which are consonant with our structures for the naturally-occurring longistrobine alkaloids. The UV spectra of the

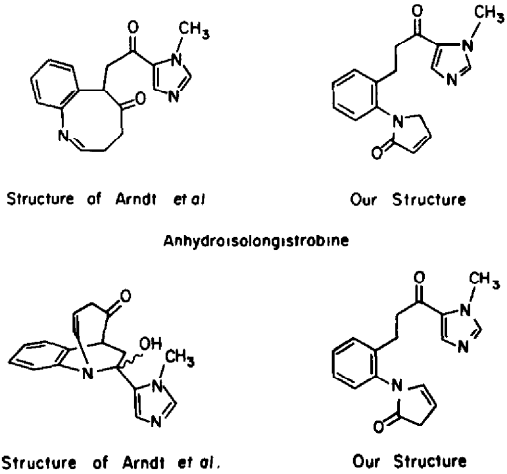


Table 2. UV spectra[5]

Compound	λ_{max} (ϵ)	λ_{max} (ϵ); Acid
Anhydrolongistrobine (HCl)	255 (21,600)	245 (22,800)
Anhydroisolongistrobine (HCl)	257 (27,200)	244 (23,200)
Anhydroisolongistrobine (DMSO)	256 (9200)	228 (11,350)

anhydro derivatives are consistent with acylimidazole structures, perturbed by the presence of the α,β-unsaturated lactam chromophore in the two anhydro compounds isolated from hydrochloric acid, in which the double bond might be expected to have shifted into conjugation (Table 2). That the anhydroisolongistrobine from dimethyl sulfoxide exchanges a proton can be readily explained by protonation of the "enamine" and subsequent deprotonation.

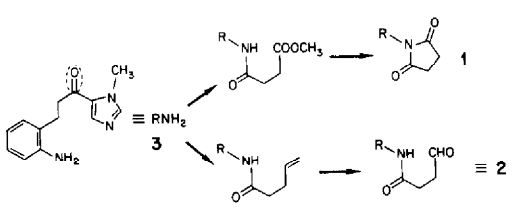
Although some of the data presented by Arndt *et al.* did not fit our proposed structures, we were confident that the evidence we had accepted was more likely to be correct than that we had rejected. In the latter category are primarily the mass spectral exchange experiments, which are incompletely described in the original paper. We were certain that the South African workers' own data ruled out the structures they had proposed.

We set out, then, to prove our hypothesis by synthesizing dehydroisolongistrobine and isolongistrobine, to which we had assigned structures **1** and **2**. We chose the *iso* series because both **2** and the synthetically simpler **1** are natural products (the corresponding dehydrolongistrobine was not isolated from natural sources) and because of the availability of the desired 5-carbonyl-1-methylimidazoles.

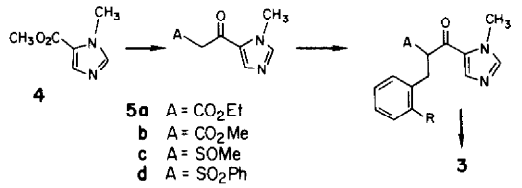
The chemistry of succinimides makes it abundantly clear that the succinimide group should be introduced at the end of any synthesis of **1**. Furthermore, a route which would allow for introduction of the succinimide group by acylation with β-carbomethoxypropionyl chloride and subsequent closure of the imide ring would be versatile. Such a route would allow for synthesis of the γ-hydroxy-γ-lactam structure of **2** from the same intermediate **3** used in a synthesis of dehydroisolongistrobine (Scheme 2).

We therefore sought to synthesize an intermediate, **3**, with an aniline group ready to participate in an acylation reaction, and with the carbonyl group alpha to the imidazole nucleus suitably rendered incapable of intramolecular cyclization. First, our attention was directed toward construction of the carbon skeleton. We chose to utilize a Claisen-type condensation with methyl 1-methylimidazole-5-carboxylate (**4**) to produce an active methylene compound **5** ready for alkylation, via its enolate anion, by a benzyl halide in which the R group could be converted into the desired aniline functionality. The synthesis of **4** from methyl sarcosinate hydrochloride had been well worked out by R. G. Jones[12] at Eli Lilly in the late 1940s: so well, in fact, that this readily-reproduced procedure is worthy of special commendation.

Claisen condensation of **4** with ethyl acetate and



Scheme 2.



5a A = CO_2Et
b A = CO_2Me
c A = SOMe
d A = SO_2Ph

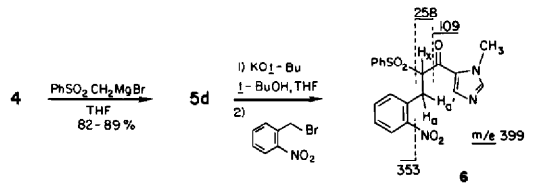
sodium hydride in tetrahydrofuran succeeded in providing **5a** in only poor yield. Similar condensation with methyl acetate and sodium hydride in tetrahydrofuran failed to produce any of the corresponding methyl ester, but when **4** was condensed with methyl acetate and sodium hydride in dimethyl sulfoxide, a small quantity of **5b** could be obtained.

Having failed to discover conditions practical for synthesis of **5** by conventional Claisen condensation, we next turned to "dimsyl" anion (sodium methylsulfinylmethide), so successfully applied by Corey[13,14] to the synthesis of methyl ketones from esters. We were able to prepare the β-ketosulfoxide **5c** in an impure state, but the reaction was found to be difficult to reproduce. Even had favorable conditions for the dimsyl anion procedure been discovered, our situation would not have been much improved: the significant water solubility of **5c** precluded its facile separation from dimethyl sulfoxide. It was nonetheless encouraging that the relatively unreactive carbonyl group of **4** could be persuaded to engage in condensation reactions of the Claisen type. We were delighted to find that Stetter and Hesse[15] had carried out a number of condensations of phenylsulfonylmethyl anion with various esters. This reaction proceeds in a tetrahydrofuran medium, thereby avoiding the dimethyl sulfoxide which of necessity accompanies dimsyl anion in its reactions.

When **4** was treated with phenylsulfonylmethyl magnesium bromide (prepared by metal-hydrogen exchange between ethyl magnesium bromide and methyl phenyl sulfone) according to the reported general procedure,[15] the β-ketosulfone **5d** was obtained in excellent yield. Methyl phenyl sulfone, a crystalline solid, can readily be obtained in an anhydrous state. This fact, coupled with the technical expedience of conducting any reaction in tetrahydrofuran rather than dimethyl sulfoxide, makes the use of Stetter and Hesse's seldom-used procedure far preferable to the dimsyl anion procedure.[16]

We had armed ourselves with a technically outstanding preparation of **5d**, and we decided that the next attack in our synthetic battle must be the alkylation of **5d**. We first demonstrated the feasibility of such a reaction in our system by treating the enolate generated from **5d** (using potassium t-butoxide) with methyl iodide.[17] The organic product, while contaminated with starting material, showed in the nuclear magnetic resonance spectrum a three-proton doublet at δ1.58 ($J = 7$ Hz) and a corresponding one-proton quartet at 4.77, indicating that the desired C-methylation product had been formed. (The methylene group of **5d**, for comparison, resonates at δ4.57 in the NMR spectrum.)

When a warm solution of the enolate of **5d** (generated



with one equivalent of potassium t-butoxide in t-butyl alcohol under argon) in tetrahydrofuran was treated with *o*-nitrobenzyl bromide and allowed to stir at 60° overnight, the alkylation product **6** could be isolated by plate chromatography. When one equivalent of base was used, the reaction reached a steady state of incomplete reaction (as judged by TLC, see Experimental) after about 5 hr. When greater than one equivalent of base was used, a deep red color was produced upon addition of the alkylating agent. Although the mode of decomposition of *o*-nitrobenzyl bromide with base was not investigated, it was found to be expedient to use only one equivalent of base in order to avoid the highly colored reaction mixtures which resulted from decomposition of the alkylating agent. This situation may also be the result of formation of O-alkylated product, which would revert to starting materials upon examination by TLC or when worked up.

Experimentally, however, there was no difficulty in isolating pure **6** without chromatography. When the residue of the concentrated reaction mixture was taken up in methylene chloride and extracted with a defined amount of aqueous sodium hydroxide, **5d** was removed as its enolate. The residue of the organic phase, upon crystallization from absolute ethanol, provided **6** in about 60% yield. Chromatography of the mother liquors allowed the isolation of additional **6**, resulting in a total yield of 70–75%. The structure of **6** was established by spectral means. The NMR spectrum, besides an N-methyl group at δ3.82 and eleven aromatic protons, showed two one-proton doublets at δ3.64 (J = 8 Hz) and 3.65 (J = 6 Hz) representing the diastereotopic protons H_a and $H_{a'}$, and a corresponding one-proton doublet of doublets at 5.20 for H_x. The mass spectrum showed a parent ion (P) at *m/e* 399, and peaks at *m/e* 353 (P − NO_2), 258 (P − $PhSO_2$), and 109 (**7**).

Our carbon skeleton had been constructed; our next task was to transform this readily-prepared material (*ca.* 15% in seven steps from sarcosine) into our carbonyl-protected aniline derivative, **3**, suitable for further elaboration into **1** and **2** (Scheme 2). We planned to reduce both the aromatic nitro group[18] and the phenylsulfonyl group[19] with aluminum amalgam. We hoped that the carbonyl group would be reduced, as well. Aluminum amalgam is known, for example, to reduce diethyl oxalacetate to diethyl malate.[20]

When **6** was subjected to the reduction conditions of Corey and Chaykovsky,[14] a mixture of two products, separable by plate chromatography on silica gel, was obtained. Each product was routinely obtained as an off-white, brittle foam, which could conveniently be used in subsequent manipulations. The more mobile of the two compounds was shown to be tetrahydroisomacrorine, **8**. Its NMR spectrum is compared below (Table 3) with that of tetrahydromacrorine (**9**)[2], and argues in favor of its tetrahydroquinoline structure, as does its UV spectrum, compared with that of **9** in Table 4. The mass spectrum of **8** is, as well, strikingly similar to the published[21] mass spectrum of **9** (Fig. 1).

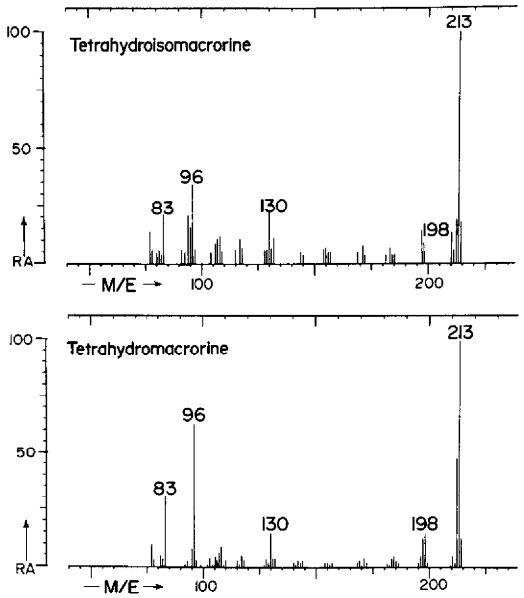


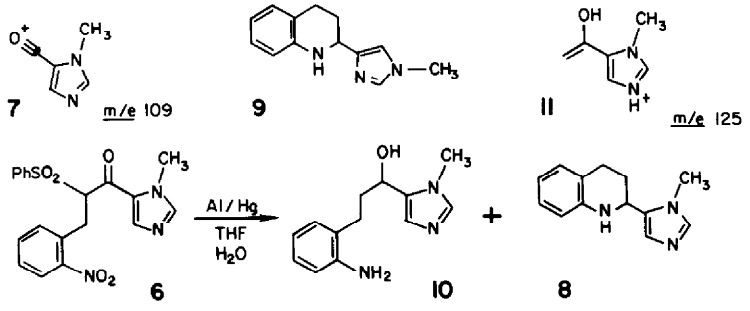
Fig. 1. Mass spectra of tetrahydroisomacrorine (**8**) and tetrahydromacrorine[20] (**9**).

Table 3. NMR spectra of tetrahydroquinolines **8** and **9** ($CDCl_3$)

Tetrahydroisomacrorine		Tetrahydromacrorine[2]
δ 2.08 (m)	$-CH_2-$	2.15 (m)
2.82 (m)	$-CH_2-$	2.80 (m)
3.58 (s)	$\underline{N}-CH_3$	3.54 (s)
4.42 (d,d)	CH	4.47 (qr)
4.42 (exch)	NH	4.30

Table 4. UV spectra of **8** (MeOH) and **9** (95% EtOH)

Tetrahydroisomacrorine	Tetrahydromacrorine[2]
205 (19,800)	207 (27,280)
248 (6650)	250 (8590)
299 (1950)	301 (2210)

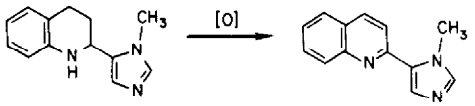


Tetrahydroquinoline **8** could be transformed into a crystalline N-acetyl compound which had correct elemental composition and appropriate spectral characteristics. Further chemical confirmation of the tetrahydroquinoline structure of **8** was secured by dehydrogenating it to form the known alkaloid, isomacrorine (*vide infra*).

The less mobile of the two products of the aluminum amalgam reduction was found to possess structure **10**. Its NMR spectrum (in $CDCl_3$) showed two two-proton multiplets at δ2.12 and 2.65, and N-methyl group at 3.50, six aromatic protons between 6.5 and 7.2, and a broad four-proton absorption at 4.50, which collapsed to a one-proton multiplet upon addition of deuterium oxide. The UV spectrum of the amino alcohol **10** is compared (Fig. 2) with that of an equimolar mixture of *o*-ethylaniline and 1-methylimidazole. The IR spectrum of **10**, as a smear on a sodium chloride plate, displayed a broad band between 3500 and 2800 cm^{-1}. A weak parent ion, with an exact mass corresponding to $C_{13}H_{17}N_3O$ (**10**), at *m/e* 231 was observed in the mass spectrum. A fragment at *m/e* 213 attested to its loss of water, while a prominent ion at *m/e* 125 was readily formulated as **11**, the result of cleavage of the benzylic bond of **10**.

In the aluminum amalgam reduction described, the tetrahydroquinoline **8** was formed in 10–30% yield, and the amino alchol **10**, in 55–75% yield when the reaction was performed at 0°. At higher temperatures (*ca.* 60°) the yields were about 40% of each product. Yields were quite variable, presumably due to the heterogeneity of the reaction.

The minor product, **8**, of the aluminum amalgam reduction described in detail above is the tetrahydro derivative of isomacrorine (**12**), reported by Arndt *et al.* in 1964,[2] and synthesized by the same workers in 1965.[3] We had noticed a highly fluorescent spot in the thin-layer chromatograms of our reduction mixtures, and when the structure of **8** had been established, we determined the UV spectrum of the fluorescent by-product, hoping that it would prove to be the oxidation product of **8**, the natural product **12**. We were not disappointed, for the UV spectrum of the fluorescent by-product agreed with that reported[2] for isomacrorine, **12**. To prepare **12** practically, we decided to subject **8** to the dehydrogenation conditions advocated by Blair *et al.*[22] Palladized charcoal is used as the catalyst, while sulfur is concomitantly reduced to hydrogen sulfide. This is a particularly good procedure, since the completion of the reaction is conveniently indicated by the cessation of hydrogen sulfide evolution. When **8** was heated in boiling xylene with powdered sulfur



8 **12** Isomacrorine

and palladized charcoal for 24 hr, the alkaloid isomacrorine (**12**) was obtained in 57% yield. After sublimation and recrystallization a sample with m.p. 105–107° (lit.[2] m.p. 110°) was obtained. The monoperchlorate salt, m.p. 204–205.5°, showed appropriate elemental composition. The diperchlorate salt had m.p. 294–307° (lit.[2] m.p. 290°) and also gave a correct microanalysis.

The NMR spectrum of isomacrorine was not reported by its discoverers, even though they reported the isolation of 6.7 g of the alkaloid from the plant. It may, however, be enlightening to compare the nuclear magnetic resonance spectrum of **12** with that reported[2] for macrorine (**13**). The comparison is made in Table 5. The UV (Table 6) and mass (Fig. 3) spectra of **12** are compared with those reported[2,20] for natural isomacrorine.

The synthesis of isomacrorine was not an object of this research. We were fortunate, in a sense, that our aluminum amalgam reduction provided the minor product **8**, for we were not only able to synthesize isomacrorine, but we could correlate it with isolongistrobine (**2**), since both were to be synthetically derived from an imidazole of a given substitution pattern (namely, **4**).

The tendency of anilines to be acylated in preference to alcohols made us confident of our ability to complete a synthesis of dehydroisolongistrobine (**1**) along the lines presented in Scheme 2. It can be seen that **10** fits the

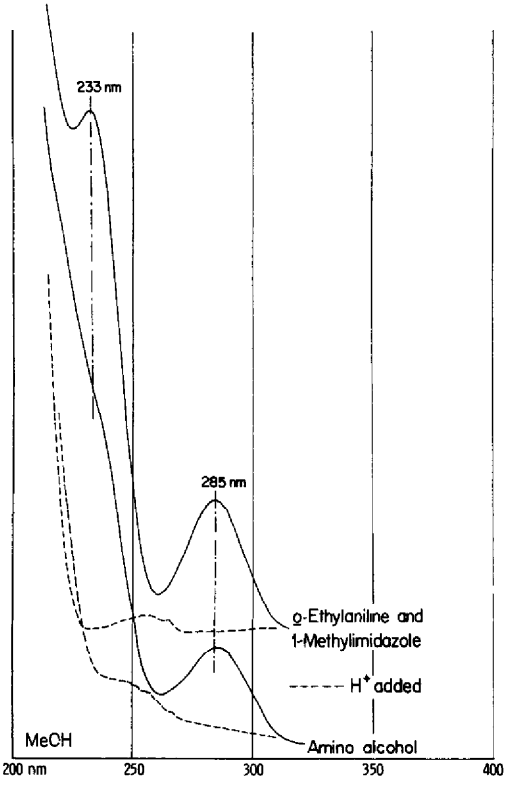


Fig. 2. UV spectra of amino alcohol (**10**) and a mixture of 1-methylimidazole and *o*-ethylaniline (vertical scale offset).

Table 5. NMR spectra of isomacrorine (**12**) and macrorine (**13**) ($CDCl_3$)

Isomacrorine		Macrorine[2]
δ 4.05 (s)	N-CH_3	3.70 (s)
7.3-8.1 (m)	aromatic	7.3-8.2 (m)

Table 6. UV spectra of isomacrorine (**12**) (95% EtOH)

	Synthetic	Natural[2]
	210 (28,300)	214 (27,820)
	234 (13,300)	235 (12,930)
	267 (23,700)	269 (28,460)
	326 (9750)	328 (11,130)
	341 (9510)	342 (11,410)
Acid Added:	213 (27,900)	218 (21,480)
	251 (33,200), 256 (32,300)	252 (37,370)
	318 (6150)	319 (7060)
	332 (5330)	334 (6410)

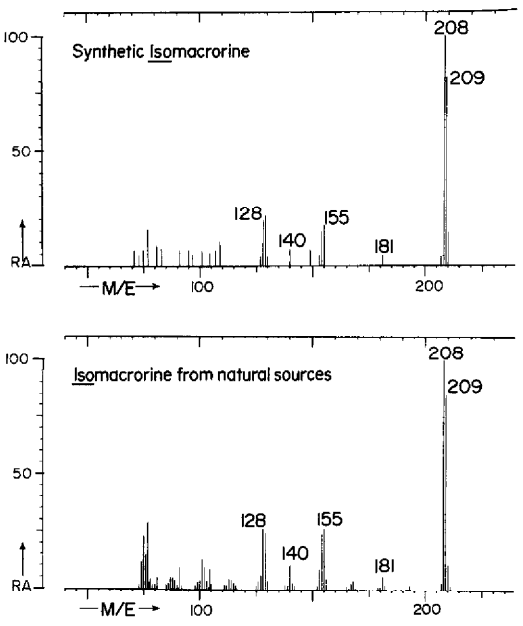


Fig. 3. Mass spectra of synthetic and natural[20]isomacrorine (12).

requirements originally embodied in the symbolic structure **3**, for **10** cannot cyclize as an unprotected **3** could (and presumably does, in the formation of **8** from **6**). The aluminum amalgam reduction of **6** had served to remove the phenyl sulfone, reduce the nitro group, and *protect the carbonyl group*, all in one step. If **10** were to be acylated on nitrogen, the secondary hydroxyl group could be oxidized to a ketone without danger of cyclization, the nucleophilicity of the nitrogen having been decreased.

The amino alcohol **10** was treated at 0° with one equivalent of β-carbomethoxypropionyl chloride in methylene chloride containing an equivalent of pyridine. The amido ester **14** exhibited a broad band at 3300 cm^{-1} in its IR spectrum (NH and OH), an ester band (1735), and secondary amide bands (1665 and 1530).

When **14** was oxidized with chromic anhydride in aqueous pyridine (Cornforth's reagent[22]) the ketone **15**, a nicely crystalline substance, was obtained in fair yield. The presence of the imidazolyl ketone function was demonstrated by mass and UV spectra. In addition to a parent ion (P) at *m/e* 343, fragments at *m/e* 256 (P − $CH_2CH_2CO_2CH_3$), 234 (P − 109), 110 (109 + H), 109 (**7**), and 82 (**16**) were observed. A strong UV maximum at 254 nm (ϵ 16,100) shifted to 232 nm (ϵ 15,900) in acid. This is to be compared with the UV behavior of **5d**, **6**, and the natural products **1** and **2**.

When **15** was heated at 200° *in vacuo* for a short time, it smoothly expelled a molecule of methanol and provided the imide **1** in high yield. The synthetic compound **1** melted at 130.5–131.5° (lit. m.p. 131° for dehydroisolongistrobine[5]; m.p. of an authentic sample provided by Dr. A. Jordaan and recrystallized twice, 130.5–131.5°; mixture m.p. 130–131.5°). The NMR (Table 7), UV (Table 8), IR (Fig. 4), and mass (Fig. 5) spectra of **1** and dehydroisolongistrobine were also in agreement.

It should be pointed out that confusing information appears in Ref. 5 concerning the spectral properties of dehydroisolongistrobine. Only the 1710 cm^{-1} band was reported for the IR spectrum of dehydroisolongistrobine, and the mass spectrum was reported to consist of peaks at *m/e* 311, 310, 110, 109 and 81. The mass spectra shown in Fig. 5, however, were obtained by us under identical conditions. The mass spectral and IR comparisons were carried out using a sample of the natural alkaloid kindly provided by Dr. Jordaan. With regard to the IR spectrum, let us call attention to the fact that the 1780 and 1710 cm^{-1} doublet is characteristic of succinimides.[10] We can only speculate why it was ignored by Arndt *et al.*

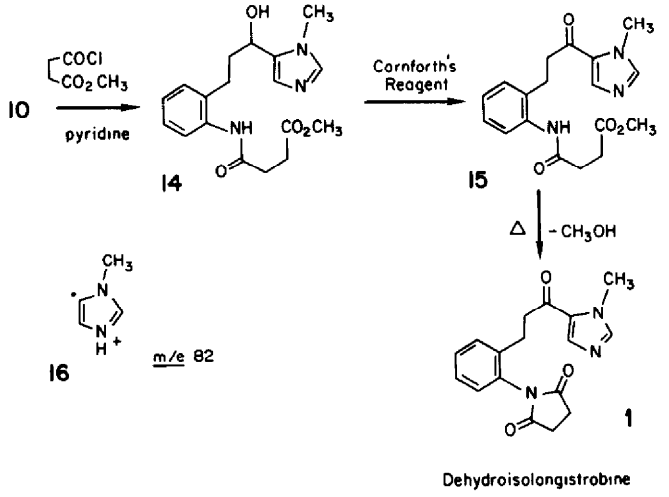
We were therefore successful in demonstrating that **1** is in fact the correct representation of dehydroisolongis-

Table 7. NMR spectra of dehydroisolongistrobine (**1**) ($CDCl_3$)

Synthetic		Natural[5]
δ 2.93 (4H, s)	succinimide	2.9 (8H, m)
2.7-3.2 (4H, m)	$ArCH_2CH_2CO$-	
3.88 (3H, s)	N-methyl	3.86 (3H, s)
7.0-7.4 (4H, m)	aromatic	7.0-7.3 (4H, m)
7.53 (1H, s)	imidazole	7.51 (1H, s)
7.74 (1H, s)		7.72 (1H, s)

Table 8. UV spectra of dehydroisolongistrobine (**1**) (95% EtOH)

	Synthetic	Natural[5]
	258 (17,000)	258 (17,350)
Acid Added:	235 (13,300)	235 (14,350)



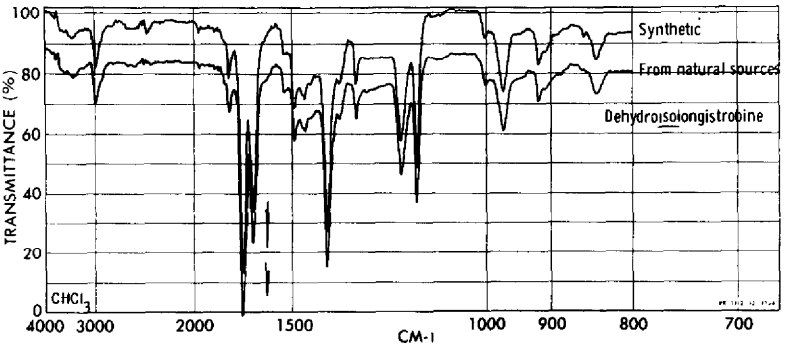


Fig. 4. IR spectra of dehydroisolongistrobine (1).

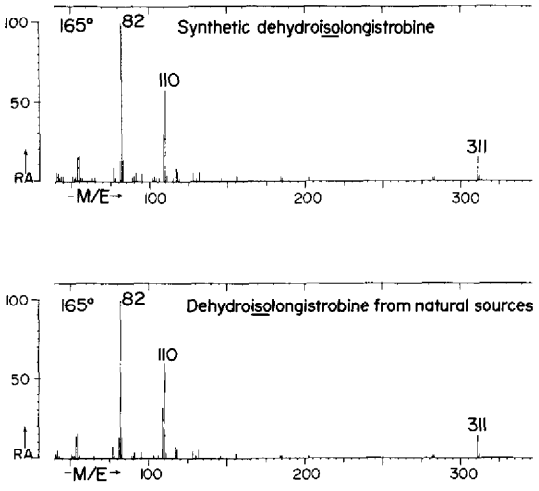


Fig. 5. Mass spectra of dehydroisolongistrobine (1).

trobine, as postulated above. We had refuted[23] the erroneous structure proposed for dehydroisolongistrobine by the South African workers. It remained to substantiate our structure **2** for isolongistrobine.

The synthesis of **2** was carried out according to the plan outlined in Scheme 2. The first two reactions, acylation of the aniline **10** with 4-pentenoyl chloride to provide **17** and subsequent oxidation to the 5-acyl-1-methylimidazole **18**, proceeded without event. These two steps are entirely analogous to those used in the preparation of **15** from **10** via **14**. In accordance with its imidazolyl ketone structure, **18** exhibited mass and UV spectra similar to those observed for its counterpart, **15**.

Low-temperature ozonolysis of **18** proceeded in poor yield. When a zinc and acetic acid workup was used, a small amount of material with thin-layer chromatographic and mass spectral behavior identical to natural isolongistrobine was obtained. We felt that perhaps the ozone was oxidizing the imidazole ring or otherwise indiscriminately assulting our vinyl compound, **18**. Therefore we sought a more readily controlled method for cleaving the terminal vinyl linkage to an aldehyde, equivalent to **2**.

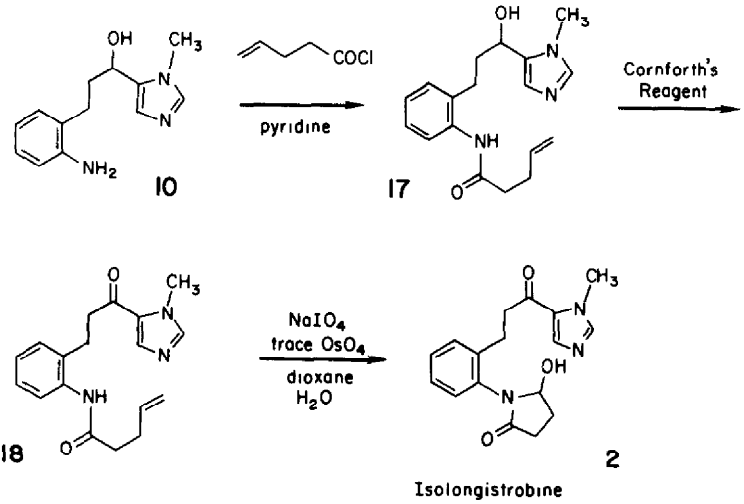
Application of the osmium tetroxide-catalyzed periodate cleavage[24] to **18** was successful. In aqueous dioxane, **18** was cleaved to provide **2** in better than 80% yield, m.p. 134–139° (lit. m.p. 132–136° for isolongistrobine[5]). Compound **2** was shown to represent isolongistrobine by direct spectral comparison with an authentic sample generously provided by Dr. Jordaan (Figs. 6–8; Table 9).[25]

We have succeeded in demonstrating that **1** and **2** are the correct structures for dehydroisolongistrobine and isolongistrobine, respectively. The carbon skeleton of

Table 9. UV spectra of isolongistrobine (2) (95% EtOH)

	Synthetic	Natural[5] (*)
	257 (15,300)	253 (16,750)
Acid Added:	232 (13,200)	235 (14,900)

*On our instrument, natural isolongistrobine exhibited an ultraviolet maximum at 257 nm which shifted to 232 nm upon addition of acid.



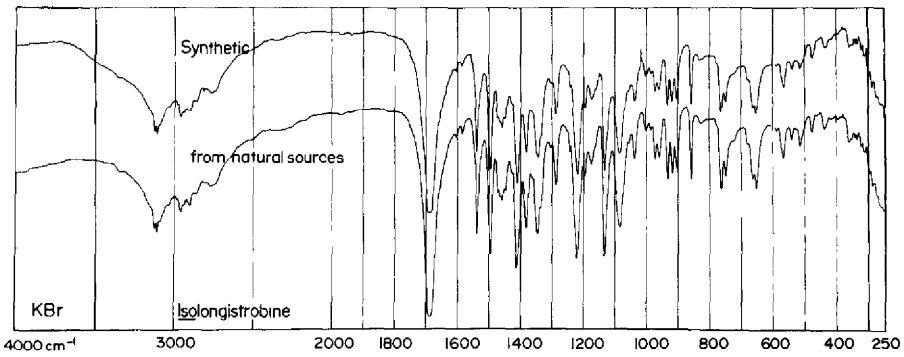


Fig. 6. IR spectra of isolongistrobine (2).

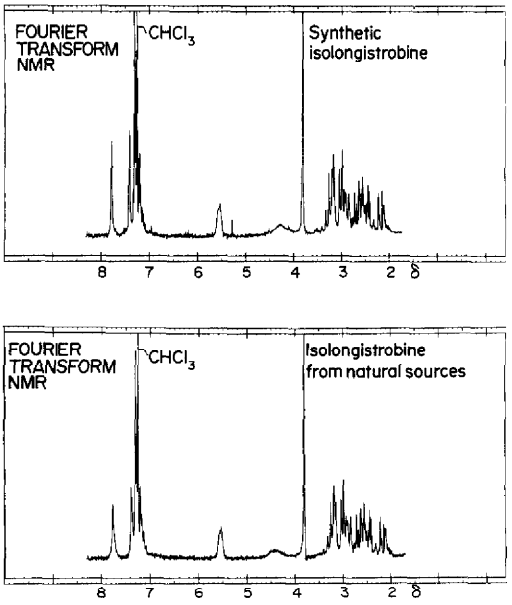


Fig. 7. NMR spectra of isolongistrobine (2) ($CDCl_3$).

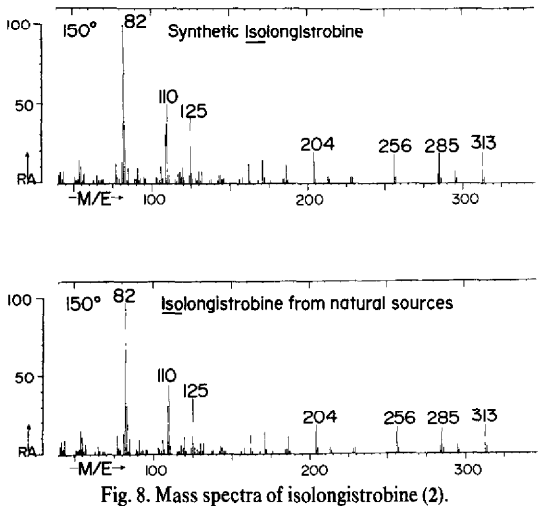


Fig. 8. Mass spectra of isolongistrobine (2).

these longistrobine alkaloids has therefore been proven beyond doubt. Furthermore, we are confident that the structures of longistrobine, dehydrolongistrobine, and the various anhydro degradation products are those proposed above.

Arndt *et al.* postulated attachment of the four-carbon succinic acid chain to the benzylic carbon, disregarding clear-cut spectral evidence, in order to accommodate their mass spectral labeling data. The discord between the data presented and the structure postulated for dehydroisolongistrobine caused us to question all the South Africans' structures and, ultimately, to disprove those structures by total synthesis.

EXPERIMENTAL

NMR spectra were obtained using Varian T-60, A-60, HA-100 and XL-100 instruments. Chemical shifts are reported in ppm downfield from internal TMS (δ). IR spectra were measured on Perkin-Elmer 137 and 457A instruments. IR frequencies are reported in wavenumbers (cm^{-1}). UV spectra were measured on a Cary Model 14 spectrophotometer. Acid spectra were obtained by adding *ca.* 10 μl of 1N HCl to the 3 ml sample cell. Absorption maxima are reported as wavelength (in nm) followed by the molar extinction coefficient (ϵ) in parentheses. Mass spectra (MS) were determined on an AEI MS-9 double-focusing instrument at 70 eV utilizing direct insertion. M.ps (Kofler block) and b.ps are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark.

Analytical TLC was carried out using Eastman "Chromagram" sheets of silica gel containing a 254 nm indicator. Preparative layer chromatography was effected on unactivated silica gel plates, prepared according to the directions of the manufacturer, E. Merck, from silica gel containing a 254 nm indicator.

"Reduced pressure" is taken to mean the vacuum obtained using a water aspirator; solvents were removed with the aid of a Büchi Rotavapor-R. "*In vacuo*" is taken to mean 0.01–0.5 torr, the vacuum reached using an ordinary oil pump.

Reagents and solvents were ordinary commercial grades, unless otherwise specified, and with these exceptions: *p*-Dioxane and tetrahydrofuran were distilled from lithium aluminum hydride (LAH) and then freshly distilled from LAH again before use; dry ether was Mallinckrodt anhydrous, freshly-opened; ether, chloroform, and methylene chloride were technical grades, once distilled; hexane was Phillips n-hexane; methanol and ethyl acetate were Mallinckrodt anhydrous and reagent, respectively, once distilled; molecular sieves were Linde 3A, activated 3 hr at 325°; potassium was cleaned at 70° under 4:1 xylene—t-amyl alcohol; t-BuOK was prepared from K and t-BuOH which had been distilled from t-BuOK.

Methyl sarcosinate hydrochloride. Sarcosine (35.6 g, 0.400 mol) in 1.5 l. MeOH was treated carefully with 180 ml $SOCl_2$,[26] added through a dropping funnel. When the addition was complete, the mixture was refluxed on the steam bath for 3 hr. The resulting mixture was concentrated under reduced pressure, and traces of $SOCl_2$ were removed by diluting several times with benzene and reconcentrating. The resulting solid was washed with dry ether and dried overnight in a desiccator at 0.05 torr to give 51.5 g (0.374 mol, 93.6%) of the sarcosine methyl ester hydrochloride; NMR (D_2O) 2.83 (3H, s, N–CH_3), 3.90 (3H, s, –CO_2CH_3), 4.08 (2H, s).

Methyl 1-methyl-5-imidazolecarboxylate (4). Methyl 1-methyl-5-imidazolecarboxylate was prepared from methyl sarcosinate

hydrochloride by the method of R. G. Jones.[17] **4** showed the following spectral properties: IR (KBr) 1710. UV (MeOH) 233 (10,700); acid, end absorption only. NMR ($CDCl_3$) 3.93 (3H, s), 4.00 (3H, s), 7.70 (1H, broad s), 7.83 (1H, broad s). MS *m/e* 140 (parent, 95%), 109 (base), 81 (30%), 54 (40%).

1-Methyl-5-phenylsulfonylacetylimidazole[15] (**5d**). To Mg turnings (3.65 g, 0.150 g-at) in 450 ml of dry ether in a flame-dried 1 l. 3-neck flask equipped with a septum cap, a reflux condenser topped by a distilling head, a dropping funnel, a magnetic stirrer, and a heating mantle, were added via syringe 11.3 ml (0.15 mol) of EtBr (stored over molecular sieves). The Grignard reaction was initiated by playing a flame about the bottom of the flask. When reflux stopped (after about 2 hr), 150 ml of THF were added, followed by 23.4 g (0.150 mol) of methyl phenyl sulfone[27] in 150 ml of THF. The mixture was distilled until the head reached a temp. of 55°, refluxed for 5 min, and cooled to ambient temp.

Methyl 1-methylimidazole-5-carboxylate (7.00 g, 0.0500 mol) in THF (75 ml) was added. The mixture was refluxed overnight (19.5 hr). After addition of 15 ml of glacial AcOH, solvent was removed under reduced pressure and the remaining paste was partitioned between water (45 ml) and $CHCl_3$ (500 ml). The aqueous phase was washed with $CHCl_3$ (150 ml), and the $CHCl_3$ layers were divided into two parts. Each was extracted with 3% NaOH (first with 225 ml, then with 125 ml). The *combined* $CHCl_3$ layers were then extracted with a further 100 ml of the base. The combined aqueous layers† were neutralized with glacial AcOH and divided into two parts. Each was extracted with CH_2Cl_2 (first with 350 ml, then with 250 ml), and the combined organic layers were dried over Na_2SO_4. Removal of solvent, followed by dissolution in boiling EtOAc (500 ml) and concentration to 350 ml, gave **5d**. Three crops were collected, totalling 11.51 g (0.0436 mol, 87.2%).

Chromatography of the mother liquors on 65 g of Woelm Activity I silica gel (elution with EtOAc–MeCN mixtures) afforded an additional 218 mg of **5d** upon crystallization from EtOAc. The yield can thereby be raised to 0.0444 mol (88.8%).

The analytical sample was recrystallized three times from EtOAc and dried (24 hr, 0.05 torr), m.p. 169–170.5°. (Found: C, 54.41; H, 4.65; N, 10.49; S, 12.08. Calc. for $C_{12}H_{12}N_2O_3S$: C, 54.54; H, 4.58; N, 10.60; S, 12.11%).

IR (KBr) 1660, 1350, 1315, 1300, 1150. UV (MeOH) 265 (15,400); acid, 246 (12,100). NMR ($CDCl_3$) 3.90 (3H, s), 4.57 (2H, s), 7.5–8.1 (7H, m). MS *m/e* 264 (parent, 25%), 200 (45%), 109 (base, $C_5H_5N_2O$), 107 (95%, $C_6H_7N_2$), 95 (40%, $C_5H_7N_2$), 77 (75%).

1-Methyl-5-(α-phenylsulfonyl-β-[o-nitrophenyl] propionyl)-imidazole (**6**). Under an argon atmosphere in a flamed flask equipped with a rubber septum and a magentic stirring bar, **5d** (1.056 g, 4.00 mmol) was dissolved in 50 ml THF at 60°. Upon dissolution, t-BuOK in t-BuOH (0.32M, 12.5 ml) was slowly syringed in. If the addition is too fast, the resulting suspension becomes too viscous to be stirred. After the addition was complete, the suspension of enolate was allowed to stir at 60° for 20 min. *o*-Nitrobenzyl bromide (*CAUTION! LACHRYMATOR*) (0.864 g, 4.00 mmol) was added very slowly via syringe as a soln in about 5 ml THF; stirring at 60° was continued overnight.

Solvent was removed from the mixture under reduced pressure, and the residue was partitioned between CH_2Cl_2 (300 ml) and 0.1N NaOH (70 ml). The latter removes unreacted starting material in preference to product.‡ The organic phase was passed through a column of Na_2SO_4, the solvent was removed under reduced pressure, and the residue was taken up in 20 ml of hot abs EtOH. In this manner, 966 mg (60.5%) of crystalline product were obtained.

The mother liquors were subjected to preparative layer chromatography on silica gel, with EtOAc as a developing solvent. From this chromatography an additional 271 mg (17.0%) of chromatographically homogeneous product were obtained for a total yield of 1.237 g (3.10 mmol, 77.4%).

The analytical sample was recrystallized twice from abs EtOH (dissolved at 50°, cooled to 0° under an argon stream) and dried (60 hr, 25°, 0.1 torr), m.p. 131–131.5°. (Found: C, 57.04; H, 4.38; N, 10.54; S, 8.08. Calc. for $C_{19}H_{17}O_5N_2S$: C, 57.14; H, 4.29; N, 10.52; S, 8.01%).

IR (KBr) 1660, 1530, 1355, 1340, 1310, 1305, 1150. UV (MeOH) 271 (16,500); acid, 251 (15,400). NMR ($CDCl_3$) see discussion section. MS *m/e* 399 (parent, 5%), 353 (30%), 254 (30%), 109 (base).

3-(o-Aminophenyl)-1-(1-methyl-5-imidazolyl) propan-1-ol (**10**) and *2-(1-methyl-5-imidazolyl)-1,2,3,4-tetrahydroquinoline* (**8**). Aluminum foil (600 mg) was cut into strips and shaken for 30 sec in a 50 ml round-bottomed flask with 25 ml of 2% aqueous mercuric chloride soln. The aqueous soln was drained off and the amalgamated aluminum was washed with abs EtOH and then ether.[14] To it were added 30 ml THF and 3 ml water. This mixture was cooled to 0° with stirring in an ice-bath and then **6** (600 mg, 1.503 mmol), dissolved in 10 ml THF, was added very slowly (50 min). When, by TLC,§ all the starting material had disappeared (*ca.* 2 hr after the addition was completed), the mixture was filtered through Celite, the grey residue was washed with 9:1 CH_2Cl_2–MeOH (50 ml), and the filtrate and washings were stripped to provide about 375 mg of an off-white foam, after pumping at 0.05 torr overnight.

This residue was dissolved in a small amount of CH_2Cl_2 and applied to preparative plates (one 1.5 × 200 × 200 mm silica plate for each mmole of **6** used; 9:1 MeCN–MeOH eluent) and chromatographed. Two main bands were present, at R_f 0.15–0.30 and 0.30–0.45. The more mobile band proved to be **8**, contaminated with a little isomacrorine, and could be isolated as a beige foam in 10–30% yield. The less mobile band contained amino alcohol **10**. The yield of the amino alcohol, after pumping on the only slightly off-white foam overnight at 0.05 torr, was 54–78%. The variability of yields in reactions conducted, on the surface, in the same manner, is presumably related to the heterogeneous nature of the reducing agent.

The spectral properties of **8** were as follows: IR (smear) 3300. UV, NMR, MS see Discussion. **8** provided a crystalline N-acetyl compound when treated with Ac_2O-pyridine; the compound crystallized from acetone-hexane as white needles, m.p. 130–133°. IR (KBr) 1645. MS *m/e* 255 (parent, 80%, $C_{15}H_{17}N_3O$), 240 (30%), 212 (base). The yield of tetrahydroisomacrorine could be increased by carrying out the reduction in an uncontrolled fashion. All of **6** was added at once; the mixture was uncooled: the temp rose to *ca.* 60°. The structure of **8** was further substantiated by its conversion to the known natural product isomacrorine.

The amino alcohol **10** showed the following spectral properties: IR, NMR see Discussion. UV (MeOH) 233 sh (6700), 286 (1900); acid, benzenoid shoulders around 250 nm. MS *m/e* 231 (parent, 15%, $C_{13}H_{17}N_3O$), 213 (15%), 125 (base), 111 (40%).

2-(1-Methyl-5-imidazolyl)quinoline or *isomacrorine* (**12**). Tetrahydroquinoline **8** (170 mg, 0.76 mmol) was treated, in refluxing xylene for 24 hr, with 100 mg S and 50 mg 10% PdC.[21] (The odor of H_2S was noticeable already after 0.5 hr at reflux.) The mixture was filtered, and the resulting xylene soln was washed with 1N HCl (50 ml). The aqueous phase was basified to pH 8 with 1N NaOH and extracted with CH_2Cl_2 (2 × 40 ml). Removal of solvent gave 132 mg of a brown oil which was chromatographed (1 × 200 × 200 mm silica plate, 9:1 MeCN–MeOH eluent, two developments) to provide (R_f 0.43–0.69) 126 mg of chromatographically homogeneous isomacrorine, which was sublimed (100°, 0.05 torr) to give 90 mg (0.43 mmol, 57%) of white, crystalline isomacrorine. Two recrystallizations from acetone–hexane provided material m.p. 105–107°. For a discussion of the comparison with natural isomacrorine, see the discussion section. IR (smear) 1610, 1570, 1500. UV, NMR, MS see Discussion.

The *mono*perchlorate crystallized from 0.5N perchloric acid and was recrystallized twice from MeOH-water for analysis, which, with drying (24 hr, 80°, 0.05 torr) provided a sample m.p.

†By drying the remaining $CHCl_3$ layers over Na_2SO_4, removing solvent, and crystallizing from benzene, 13.09 g (84% of the excess) of methyl phenyl sulfone could be recovered.

Separations, and the reaction itself, could be conveniently followed by TLC (silica gel, ethyl acetate eluent). The R_f values were: **5d**, 0.25; *o*-nitrobenzyl bromide, 0.70; **6**, 0.35.

§The following R_f values were observed (silica gel, 9:1 MeCN–MeOH): **6**, 0.7; **8**, 0.4; **10**, 0.3.

204–205.5°. (Found: C, 50.76; H, 3.98; N, 13.78; Cl, 11.42. Calc. for $C_{13}H_{12}N_3O_4Cl$: C, 50.41; H, 3.91; N, 13.57; Cl, 11.45%).

The *di*perchlorate crystallized from 30% perchloric acid and was recrystallized twice from 30% perchloric acid. After drying (24 hr, 80°, 0.05 torr), the analytical sample melted at 294–307°. (Found: C, 37.75; H, 3.23; N, 10.16; Cl, 17.15. Calc. for $C_{13}H_{13}N_3O_8Cl_2$: C, 38.07; H, 3.19; N, 10.24; Cl, 17.29%).

3-(o-[*β-Carbomethoxypropionamido*] *phenyl*)-1-(1-*methyl*-5-*imidazolyl*) *propan*-1-*ol* (**14**). A soln of **10** (231 mg, 1.00 mmol) in CH_2Cl_2 (*ca.* 60 ml) containing 79 μl (1 mmol) of pyridine was cooled to 0°. Then β-carbomethoxypropionyl chloride† (129 μl, 1 mmol) was added slowly, with stirring. Stirring at 0° was continued for 30 min. Solvent was removed and the residue was pumped overnight before plate chromatography (1.5 × 300 × 200 mm silica plate, 9:1 acetonitrile-methanol eluent). The band at R_f 0.11–0.25 gave 219 mg (0.635 mmol, 63.5%) of amido ester **14** as an off-white foam. IR (smear) see discussion section. UV (MeOH) end absorption only, $\epsilon^{250} = 2{,}980$. MS *m/e* 345 (parent, weak), 125 (base).

5-(*β*-[o-(*β-Carbomethoxypropionamido*) *phenyl*] *propionyl*)-1-methylimidazole (**15**). To a soln of **14** (219 mg; 0.635 mmol) in 4 ml pyridine was added Cornforth's reagent[22] (2.23 ml, 1 equiv). The mixture was stirred overnight under argon, diluted with water (80 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The dried CH_2Cl_2 extracts were evaporated; pyridine was removed by cooling the receiver of the rotary evaporator with liquid N_2. Passage of a 9:1 MeCN–MeOH soln through 10 g of silica gel (Woelm Activity I) gave 133 mg of an oil which was chromatographed (0.5 × 200 × 200 mm silica plate, 9:1 MeCN–MeOH eluent) to give 94 mg (0.27 mmol, 43%) of chromatographically homogeneous ketone **15**.

For analysis, a sample was recrystallized four times from CH_2Cl_2–hexane and dried (30°, 72 hr, 0.05 torr), m.p. 119.5–121°. (Found: C, 62.77; H, 6.22; N, 12.33. Calc. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24%).

IR (KBr) 3300, 1735, 1660 (imidazolyl ketone), 1655 and 1530 (secondary amide). UV (MeOH) see discussion section. NMR ($CDCl_3$) 2.83 (4H, s, $-COCH_2CH_2CO-$), 2.99 (2H, t, $J = 6$ Hz, $-COCH_2CH_2$Ar), 3.26 (2H, t, $J = 6$ Hz, $-COCH_2CH_2$Ar), 3.73 (3 H, s, $-CO_2CH_3$), 3.92 (3H, s, N–CH_3), 7.0–7.9 (6H, m, aromatic, 8.96 (1H, broad s, NH). MS *m/e* 343 (parent, 45%), 256 (45%), 234 (30%), 110 (75%), 109 (40%, 82 (base)

1-*Methyl*-5-(*β*-[o-*succinimidophenyl*] *propionyl*) *imidazole* or *dehydroisolongistrobine* (**1**). In three separate experiments, **15** (110 mg; 0.32 mmol) was pyrolyzed. The pyrolyses were conducted by placing **15** in a tube connected to the vacuum line and immersing the tube for 5 min in an oil bath preheated to 200°. Conversion was better when crystalline starting material was used. The combined pyrolysis residues (*ca.* 2:1 **1**:**15** by NMR) were chromatographed (0.5 × 200 × 200 mm silica plate, four elutions with EtOAc). The band at R_f 0.45–0.55 gave 29 mg (26%) of starting material, while the band at R_f 0.25–0.45 afforded 61 mg (0.20 mmol, 61%; 83% considering recovered starting material) of **1**, which was crystallized from CH_2Cl_2-hexane to give white plates m.p. 129–131.5°. For a discussion of the comparison with natural material, see the text of this paper.

Two recrystallizations from CH_2Cl_2–hexane and drying (25°, 0.001 torr, 24 hr) provided an analytical sample, m.p. 130.5–131.5°. (Found: C, 65.48; H, 5.47; N, 13.37. Calc. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50%).

IR (KBr) 1780 and 1710 (succinimide), 1665 (imidazolyl ketone). UV, NMR, MS see Discussion.

4-*Pentenoyl chloride.* 4-Pentenoic acid (3.00 g, 30.0 mmol) and $SOCl_2$ (2.5 ml, *ca.* 33 mmol) were heated at 40° under a drying tube overnight. The residue was distilled at atmospheric pressure in a flame-dried apparatus. The forerun (0.316 g, b.p. 26–103°) was discarded. The main fraction, b.p. 103–122°[29] (2.62 g, 22.1 mmol, 73.7%) was 4-pentenoyl chloride. IR (liquid film) 1805, 1640. NMR ($CDCl_3$) 2.53 (2H, t, $J = 7$ Hz, $-CH_2CH_2CH$=), 3.03 (2H, t, $J = 7$ Hz, $-CH_2CH_2COCl$), 4.9–6.2 (3H, vinyl multiplet).

1-(1-*Methyl*-5-*imidazolyl*)-3-(o-[4-*pentenoamido*] *phenyl*) *propan*-1-*ol* (**17**). To a stirred CH_2Cl_2 soln (40 ml) of 324 mg (1.40 mmol) of **10** and 110 μl (1 equiv) of pyridine at 0° was added 4-pentenoyl chloride (166 μl, 1 equiv assuming $\rho = 1$). After stirring 30 min at 0°, removal of solvent and pumping overnight afforded 522 mg of a gummy foam which was chromatographed (1.5 × 500 × 200 mm silica plate, 9:1 MeCN–MeOH eluent). The band at R_f 0.07–0.25 provided 261 mg (0.833 mmol, 59.5%) of **17** as a crisp foam. IR (smear) 3300 (broad), 1660, 1530. UV (MeOH) end absorption only, $\epsilon^{250} = 4{,}440$. MS *m/e* 313 (parent, weak), 295 (5%), 125 (base).

1-*Methyl*-5-(*β*-[o-(4-*pentenoamido*) *phenyl*] *propionyl*) *imidazole* (**18**). The crude alcohol **17** was oxidized with Cornforth's reagent[22] in the same manner as **14**. After chromatography (silica plates, 9:1 MeCN–MeOH eluent) the ketone **18** was obtained in 10% yield from **10**. When alcohol **17** purified by plate chromatography was used, yields were 43% and 52% in 0.15 and 0.5 mmol runs.

Four recrystallizations from CH_2Cl_2–hexane provided a sample m.p. 105.5–107°, which was dried (24 hr, 0.05 torr, 25°) for analysis. (Found: C, 69.25; H, 6.82; N, 13.51. Calc. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50%).

IR (KBr) 3400, 1670 (imidazolyl ketone), 1685 and 1540 (secondary amide). UV (MeOH) 255 (11,000); acid, 232 (11,400). NMR ($CDCl_3$) 2.60 (4H, broad s, $-COCH_2CH_2CH$=), 2.95 (2H, t, $J = 6$ Hz, ArCH_2CH_2CO-), 3.26 (2H, t, $J = 6$ Hz, $-COCH_2CH_2$Ar), 3.89 (3H, s), 4.9–5.3 and 5.6–6.2 (2H, m, and 1H, m; vinyl multiplet), 7.0–7.9 (6H, m, aromatic), 8.95 (1H, broad s, NH). MS *m/e* 311 (parent, 10%), 256 (20%), 213 (45%), 202 (45%), 109 (base), 82 (65%).

5-*Hydroxy*-1-(o-[3-(1-*methyl*-5-*imidazolyl*)-3-*oxopropyl*] *phenyl*)-2-*pyrrolidinone* or *isolongistrobine* (**2**). To a soln of **18** (32.8 mg; 0.106 mmol) in dioxane (10 ml) and water (3 ml) was added a small crystal (1–2 mg) of osmium tetroxide.[24] When the soln turned brownish (*ca.* 10 min), 48 mg (0.22 mmol) of sodium periodate were added. When the reaction was over (after about 1.5 hr),‡ the volume of solvent was reduced to 1 ml and this residue was partitioned between water (30 ml) and CH_2Cl_2 (50 + 25 ml). The CH_2Cl_2 layers provided 28 mg (0.090 mmol, 85%) of **2**. Chromatography (silica plate, 9:1 MeCN–MeOH eluent) served to further purify **2**. For a comparison with natural material, see Discussion.

For analysis a sample was recrystallized three times from acetone–hexane and dried (18 hr, 80°, 0.05 torr), m.p. 134–139°. (Found: C, 65.12; H, 6.22; N, 13.28. Calc. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41%).

IR (KBr) 3125, 3110, 1695–1680, 1540, 1495. NMR ($CDCl_3$) 2.17–3.35 (8H, complex m, CH_2), 3.82 (3H, s), 4.29 (1H, broad, OH), 5.56 (1H, broad, CH), 7.07–7.37 (4H, m, aromatic), 7.42 and 7.79 (1H, s, and 1H, s; imidazole protons). UV, MS see Discussion.

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†IR (liquid film) 1805. NMR ($CDCl_3$) 2.70 (2H, t, $J = 7$ Hz, $-CH_2CH_2CO_2CH_3$), 3.30 (2H, t, $J = 7$ Hz, $-CH_2CH_2COCl$), 3.76 (3H, s).[29]

‡The reaction was followed by TLC (silica gel, 9:1 acetonitrile–methanol eluent); R_f values were as follows: **18**, 0.60; **2**, 0.39.

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