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The Stereospecific Total Synthesis of Haemanthidine and Tazettine[1]

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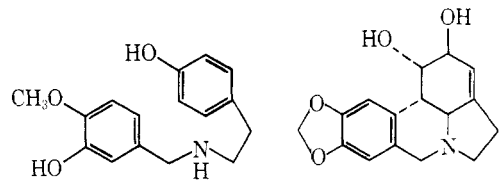
Abstract: Synthesis design principles are discussed for the crinane skeleton family of amaryllidaceous alkaloids, and a prime synthetic sequence so derived is realized in a stereospecific total synthesis of the functionally and stereochemically most complex member, haemanthidine, as well as the closely related tazettine.

Most of the structures of alkaloids can be grouped into a few large families of common skeleton and/or common biosynthesis. Of these, the large family (over 70 structures) of alkaloids of the *Amaryllidaceae* are a single biosynthetic family containing three main skeletal variants from oxidative coupling of the norbelladine (**1**) precursor;[2] the three are represented by their ubiquitous members, lycorine (**2**), galanthamine (**3**), and crinine (**4d**). At the time we initiated this work, galanthamine had been synthesized by a biomimetic route[3] and the other two had not. Natural alkaloids of the lycorine family have not yet been synthesized despite a number of efforts,[4] and two syntheses of crinine have since appeared.[5]

We elected to examine the most complex of the crinine family, *i.e.*, haemanthidine (**4a**), as the most challenging. The crinine family consists of a variety of alkaloids differing in functionality at positions 3, 6, and 11 as summarized in **4**; a parallel set exists with an added methoxyl group on the aromatic ring. In selecting haemanthidine as the primary target, we should create the most functionalized member, from which selective removal or alteration of the functional groups could lead to the other members (*cf.* **4a** → **b** → **c** → **d**). Such a route would then constitute a more general synthesis of the whole family, whereas a primary target of less functionality would require functionalization of unactivated sites (a much more difficult synthetic direction) in order to achieve the same generality. Indeed, at least in the dihydro series, such functionality removal had already been achieved by Wildman[6] during degradative studies.

The synthetic challenge is manifest both in the stereochemistry of haemanthidine and in its sensitivity to acid and base. The stereochemistry is depicted in **5**; there are five asymmetric centers marked, four centered on ring C, and the fifth, at C-6, which is selfequilibrating *via* the amino-aldehyde tautomer.[7] From a synthetic viewpoint, the axial carbon-11 mounted on a rigid *trans*-decalin skeleton affords a functional site for stereocontrol, particularly of the introduction of the less stable axial methoxyl group at C-3, equilibration of which to the more stable allylic ether should provide a route to the crinamine epimers (**4a,b**). The hydroxyl group at C-11, however, is the opposite epimer to



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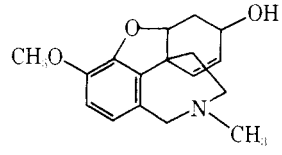

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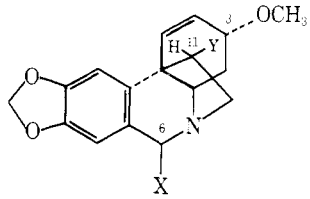
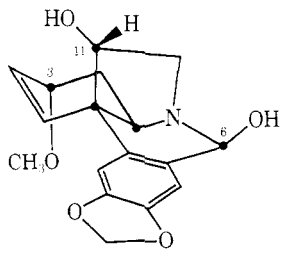


		6-X	11-Y	3-epimer
4a.	haemanthidine	OH	OH	6-hydroxy-crinamine
b.	haemanthamine	H	OH	crinamine
c.	buphanisine	H	H	
d.	crinine(3-OH)	H	H	epicrinine



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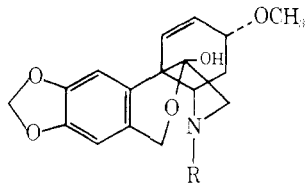
that obtained on hydride reductions of ketone in the natural series.[8,9] The sensitivity of haemanthidine to acid and base also puts severe synthetic strictures on the choice of the



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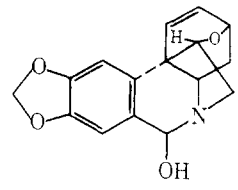

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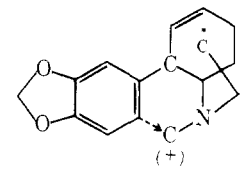

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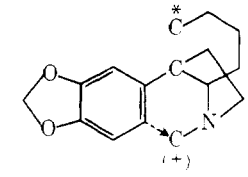

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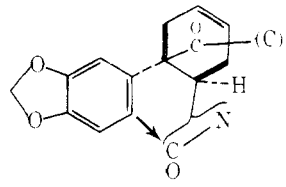

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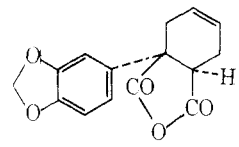

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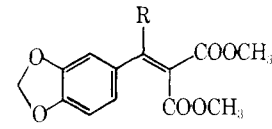
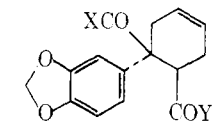
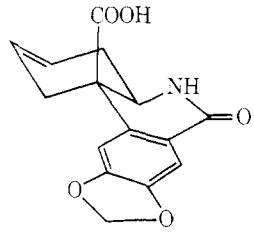


12a, R = H
b, R = CN



	X	Y
13a,	OH	N_3
b,	OH	OH
c,	OH	OCH_3
d,	OCH_3	OH
e,	OCH_3	OCH_3
f,	OCH_3	N_3



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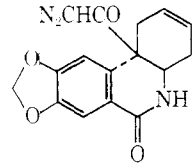

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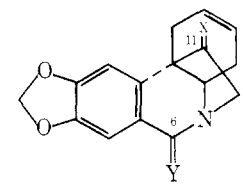
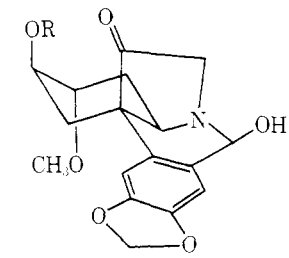
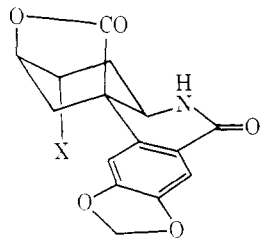


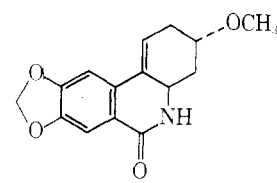
18a, X = Y = O
b, X = Y = H, OH
c, X = O; Y = H, OH



19a, R = H
b, R = SO_2CH_3



20a, X = I
b, X = OCH_3



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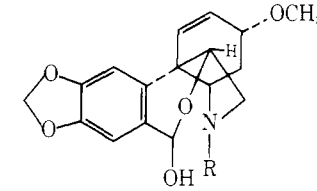


26a, R = H
b, R = C_2H_5

final steps in any sequence. In mild bases, haemanthidine is transformed into the isomeric alkaloid, nortazettine (**6**, R = H). The alkaloid tazettine (**6**, R = CH_3) has been isolated from the plant and can also be formed by heating haemanthidine with methyl iodide. The transformation is believed to involve a facile, internal Cannizzaro reduction of the C-6 aldehyde by hydride transfer from C-11 (**5**); the reaction does not occur on the C-11 epimer.[9] Acidic conditions, on the other hand, promote solvolysis of the allylic methoxyl with concomitant internal attack of the C-11 hydroxyl to form apohaemanthidine (**7**).

A skeletal approach to synthesis design focuses on two important skeletal features, the presence of a quaternary carbon and the appearance of the skeleton of the available starting material, piperonal (3,4-methylenedioxybenzaldehyde). The appearance of the latter implies construction either of the aromatic bond to the quaternary carbon or to C-6, and the precedent[4,5] is clear that electrophilic substitutions will introduce a second carbon symmetrically ortho to the first. We elected to introduce C-6 as a one-carbon electrophile delivered by the nitrogen, thus leaving the quaternary carbon as the original piperonal aldehyde carbon and necessitating construction of the other three bonds around it. Constructions creating quaternary carbons are the most restricted constructions in synthesis[10] and hence the focus of skeletal dissection here. The last construction step creates one of these three bonds, and dissection of each leaves three substrate skeletons as precursors for the last construction. One of these contains a nine-membered ring and is discarded[11] as not readily made, and the others are shown as **8** and **9**.

There are four kinds of constructions which may be used for creating quaternary centers: tertiary carbanions as organometallics or enolates; addition to tertiary double bonds, especially pericyclic reactions; oxidative coupling; and rearrangement.

Rearrangement modes may be analyzed by reconnecting the starred carbon in **8** or **9** to one of the two (nonaromatic) sites adjacent to the quaternary site and considering the requisite functionality and stereochemistry for a rearrangement of the precursor so obtained. (The same should be done for the discarded nine-ring precursor.[11]) Such analyses do not usually afford synthetically simpler precursors since they do not disconnect separate synthons; in the present instance accordingly none of the six possible rearrangement precursors appeared useful. Oxidative coupling is the mode used in biosynthesis, creating the bond to the aromatic ring from **1**, but the practical precedent for such reac-

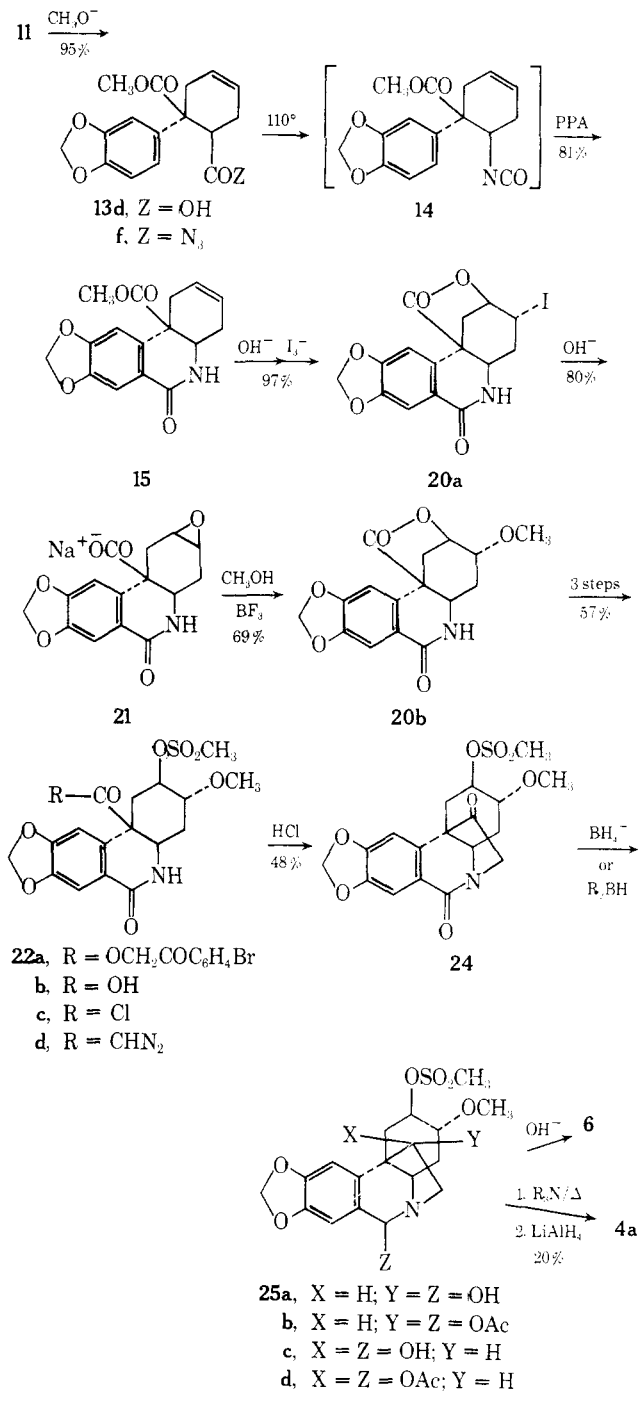
tions in the laboratory is poor.[12] The Muxfeldt synthesis[5a] utilized a pericyclic addition (Claisen rearrangement) to afford the quaternary carbon, while the Whitlock synthesis[5b] employed an enolate alkylation.

Consideration of skeletons **8** and **9** shows that only **9** can be further dissected by one bond so as to divide the carbon skeleton into two component synthons of significant size; thus, disconnection of ring C for a (2 + 4) annelation affords a 4-carbon synthon. This dissection in turn implies a Diels–Alder reaction which can create the quaternary center and has the added advantage, not realized in the other approaches, of affording as well stereocontrol of the introduction of two asymmetric centers at once and also a product functionality well suited to final functionalization of ring C. Further examination of this cycloaddition (**10**) shows that it also affords a functionalized C-11 with the electron-withdrawing carbonyl required for the dienophile. An electron-withdrawing group at the other side of the dienophile would become the nitrogen atom and hence must be either nitro or a carbonyl subsequently subject to nitrogen insertion *via* rearrangement (with stereochemical retention of configuration). We chose the latter since the required cis orientation of electron-withdrawing groups on the dienophile can be assured, and since the carbonyl extruded in the nitrogen-insertion rearrangement is then properly functionalized for attachment to the aromatic as C-6. The necessary cis geometry of the dienophile thus dictates a maleic anhydride and the cycloaddition with butadiene to anhydride (**11**) as the central construction of the synthesis, leaving only nitrogen insertion and closure of C-6 to ring B and the affixation of one bridge carbon. The above analysis therefore virtually prescribes the whole synthesis, which is outlined in Chart I.

Preparation of the phenylmaleic anhydride from piperonal was first conceived in terms of a Knoevenagel reaction (or a variant) with dimethyl malonate, which indeed produced piperonylidenemalonate (**12a,** 83%) in room temperature ethanol with piperidinebenzoate catalysis. Addition of cyanide ion was rapid, and subsequent oxidation of the product anion *in situ* by addition of chloramine-T afforded α-cyanopiperonylidenemalonate (**12b,** 49%). Alkaline hydrolysis yielded a gummy acid which in turn yielded 3,4-methylenedioxyphenylmaleic anhydride (19%) on distillation.[13] As the overall yield (8%) of this otherwise apparently economical route was unacceptable for a synthetic starting material, we turned to an arylation of maleic acid, shown in Chart II. This procedure, although it appears much longer, actually takes little more time than the "shorter" one outlined above and yields the methylenedioxyaniline hydrochloride in 82% overall yield[15] and the anhydride in 31% overall. The Diels–Alder reaction with butadiene proceeded at 120° to the central starting material, **11,** in 63% yield.

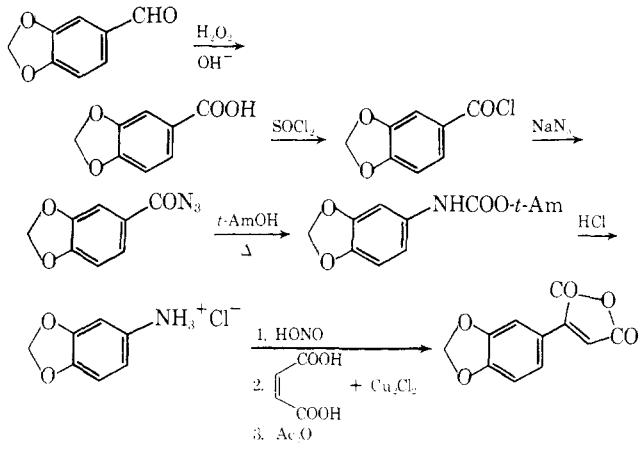
For the nitrogen insertion, we intended direct attack of azide ion on the anhydride of **11** at the less hindered carbonyl to yield directly the azide **13a** for the Curtius rearrangement. However, the anhydride was unreactive to azide ion under various conditions. Alkaline hydrolysis of **11** led to the diacid **13b** (mp 204–208°) which formed a monomethyl ester (mp 183–185°) on acidic esterification with methanol; this was assigned structure **13c** on the grounds that the less hindered ester will be formed more readily. The other monomethyl ester **13d** (mp 171–176°) was created by saponification of the dimethyl ester **13e** (mp 92–93°), obtained by diazomethane treatment of any of the acids.[16] That an isomeric ester, **13d,** was formed in this saponification was also consistent with more rapid hydrolysis at the less hindered ester group. This evidence was taken as a demonstration that the structures of the two isomeric monomethyl esters are thus correctly assigned and allows conversion of the correct **13d** to the required azide **13f.**

Chart I. Stereospecific Total Synthesis of Haemanthidine



Synthetically, the procedure was simplified by the surprising observation that treatment of the anhydride **11** with methoxide led exclusively to **13d** despite the presumption that more rapid attack of methoxide should occur at the less hindered carbonyl and afford the salt of **13c.** Apparently this kinetic product is equilibrated (*via* anhydride), and the more stable salt of **13d** is thermodynamically preferred. This preference is rationalized by the greater steric demands of the solvated carboxylate ion over the methyl ester. In any case, a further proof of the assignments lies in the conversion of **13d** to acid chloride (*via* oxalyl chloride) and azide (**13f:** ir 4.65 μ), with sodium azide in aqueous acetone, and on through the sequence without isolations to the crude isocyanate (**14:** ir 4.39 μ) by refluxing for 2 hr in toluene. This isocyanate could be cyclized to the lactam **15** by

Chart II. Synthesis of 3,4-Methylenedioxyphenylmaleic Anhydride



a variety of mild acids, and the presence in the ir spectrum of the 6.0-μ band for a six-membered lactam confirmed the assignment of **13d.** The other acid, **13c,** similarly afforded an isomeric five-membered lactam with ir 5.9 μ. Although the lactam **15** (mp 280–281°) could be prepared in moderate yield with various acids (BF_3, CF_3COOH, p-$C_7H_7SO_3H$), the best cyclization was obtained using polyphosphoric acid at room temperature (0.5 hr). That the cyclization to **15** had occurred as precedented, at the correct site on the methylenedioxyphenyl ring, was shown by the nearly unsplit para hydrogen nmr signals at δ 7.02 and 7.34, similar to those in haemanthidine and its derivatives. Saponification of **15** afforded quantitatively the corresponding acid salt, crystallized from the aqueous basic medium.

The lactam-carboxylic acid so obtained, with two asymmetric centers already fixed, provides for very clear stereocontrol of the introduction of the remaining groups and chiral centers. As shown in **16,** the rigid *trans*-decalin bicyclic bears an axial carboxyl group dominating the top side of the molecule, either over the double bond for stereocontrolled ring-C functionalization or for extension over the lactam nitrogen for bridge formation. Either of these subsequent operations might be undertaken first in the sequence, and we have tried both.

Conversion of **16** to the acid chloride was effected with thionyl chloride and the crude chloride taken directly to the diazo ketone **17** (mp 161–162°) with diazomethane in 96% yield. As implied by **16,** the diazo group lies directly over the lactam nitrogen and its electron pair so that protonation with dry hydrogen chloride yielded 6,11-dioxocrinene (**18a;** 82%, mp 217–219°) directly. Owing to Bredt's rule, the apparent lactam in **18a** can have no resonance overlap with double bond character between the nitrogen and the adjacent carbonyl. Lacking normal amide resonance, this carbonyl is much more reactive than normal amides, analogous to the 6-oxohaemanthamine derivatives in the natural series.[2,17]

The carbonyl absorbs at 5.85 μ in the infrared spectrum (the five-membered cyclic ketone at C-11 absorbs at 5.7 μ), and facile reaction with ethanol is indicated by the change in the ultraviolet spectrum (particularly loss of the band at 314 nm) after 15 hr in ethanol solution at room temperature. Also reduction of the dioxocrinene (**18a**) proceeds easily with sodium borohydride at room temperature to a mixture (about 1:1 by tlc) of diols, presumably epimeric at C-11 (**18b**); in other examples (see below), the quasi-amide carbonyl at C-6 is actually reduced faster than the ketone at C-11.

Refunctionalization of ring C can now follow construction of the bridge in **18** and will presumably be sterically directed by the rigid axial orientation of that bridge. In particular, epoxidation of the double bond on the top face, syn to the bridge, followed by trans-diaxial methanolysis, should afford one stereoisomer (**19a**) with the correct configuration for the methoxyl of haemanthidine as well as an axial hydroxyl for elimination to form the double bond. The latter can also serve to hinder hydride delivery to the C-11 ketone from the incorrect direction.

Accordingly, the C-6 carbonyl was reduced first to eliminate concern over its reactivity; this selective reduction proceeded smoothly at −20° with sodium borohydride in tetrahydrofuran to **18c** (mp 247–248°), retaining only the 5.7-μ ketone peak. Epoxidation from the more hindered side of the C-ring double bond was undertaken with iodine-silver acetate in acetic acid, followed by saponification to a crystalline iodine-free epoxide, mp 260° dec, apparently only one substance by tlc. However, when this epoxide was opened with methanolic boron trifluoride at ice temperatures, two hydroxy-methoxy derivatives were formed as shown by two methoxyl peaks in the nmr spectrum and two similar spots on tlc. As this implies that the epoxidation of **18c** had actually yielded both epimeric epoxides, we had apparently not achieved the intended stereocontrol for functionalizing ring C.

The other synthetic approach from acid **16** involves the functionalization of ring C first, utilizing the stereocontrol made available by the axial carboxyl. The acid salt was treated with iodine–potassium iodide in aqueous bicarbonate and yielded an iodolactone (**20a:** mp 268–270°; ir 5.58, 5.97 μ) with a trans-diaxial orientation of the iodide and lactone oxygen. Warmed with aqueous alkali, the iodolactone was transformed easily and stereospecifically into the salt of the epoxy acid **21,** with the epoxide group cis to the carboxyl, and this in turn when stirred with methanolic boron fluoride yielded the trans-diaxial methoxylactone (**20b:** mp 274–275°; ir 5.66, 5.97 μ), now bearing the correct axial stereochemistry at C-3 and an axial oxygen at C-2 oriented for only one possible trans-diaxial elimination to the correct Δ^1 position for the olefin in haemanthidine.

In order now to free the lactone carboxyl for the nitrogen bridging procedure used before, it was first saponified to the hydroxy acid salt, which reverted spontaneously to lactone on acidification. In order to prevent this and also convert the 2-hydroxyl to a leaving group for elimination, the acid salt was esterified by displacement on p-bromophenacyl bromide in dimethylformamide at room temperature, and the crude (crystalline, mp 151–157°) ester was mesylated with methanesulfonyl chloride in pyridine to the mesyl ester **22a** (mp 232–233°). This mesylate (**22a**) was isolated in only 55% yield, but 11% methoxylactone (**20b**) was also separated, indicating some relactonization by pyridine catalysis. Attempts to achieve both elimination and saponification by heating **22a** with alkali, however, yielded only the decarboxylated olefin **23.** This implies that the expected olefinic acid was, in fact, obtained but that the axial carboxyl with a β,γ-double bond is ideally suited stereoelectronically for a facile pericyclic decarboxylation. Furthermore, eliminations attempted on **22a** with *tert*-butoxide yielded substantial amounts of methoxylactone (**20b**), apparently by proton removal from the mesylate, elimination of the C-2 alkoxide, and internal lactonization.[18] However, in view of the poor stereospecificity of hydride reduction at C-11 in the natural derivatives,[8] there was presumed value in retaining the axial mesylate at C-2 to hinder later hydride approach to a ketonic C-11 from the unnatural side (see **19b**). Hence the mesylate was retained to foster this stereocontrol of the C-11 site at a later stage.

Saponification of the ester in **22b** could be achieved with-

out loss of the mesylate using powdered potassium hydroxide in room-temperature tetrahydrofuran, and the resultant crude acid **22b** (mixed with *p*-bromobenzoic acid) was converted to the crystalline acid chloride (**22c:** mp 191–193°; λ_{ir} 5.58, 5.98 μ). This unusually unreactive acid chloride required several days with diazomethane in dioxane and some potassium carbonate catalysis to convert to the diazo ketone **22d** (mp 172–173°; λ_{ir} 4.72, 6.01 μ). As before, treatment with dry hydrogen chloride[20] created (55% yield) the bridged ketone quasi-amide **24** (mp 193–195°; ir 5.68, 5.85 μ; in the series of compounds **22** and **24,** the mesylate sulfonyl was evidenced by ir 7.5 and 8.5 μ). These transformations to the key **24** create the full crinane skeleton with complete stereochemical control and generally clean reactions resulting in an overall yield of 15% from the ester **15** to **24.**

The final steps from **24** to haemanthidine are conceptually simple: hydride reduction of the two carbonyls, presumably with correct stereospecificity at C-11 owing to the axial mesylate hindrance at C-2; protection of the hydroxyls to prevent the base-catalyzed tazettine rearrangement during mesylate elimination; and deprotection to haemanthidine. The hindrance of C-11 was quickly demonstrated by room-temperature reduction of **24,** which yielded only a monoketone, **19b** (ir 5.69 μ), using sodium (or lithium) borohydride in 2-propanol for as long as 2 days.[21] In refluxing 2-propanol, however, both carbonyl bands disappeared in the infrared spectrum and subsequent treatment with hot methanolic alkali yielded exclusively nortazettine (**6**), identical with a sample prepared from natural haemanthidine[22] when compared by tlc or by ir and nmr solution spectra. No evidence of 11-epihaemanthidine was found by tlc comparison, thus indicating the success of stereocontrol by the hindering axial group at C-2 and complete reduction of **24** to the correct epimer **25a** before elimination.

It now remained to protect the hydroxyls before elimination in order to prevent the internal Cannizzaro hydride transfer and secure haemanthidine itself. Acetylation of the hot borohydride product, with either pyridine or boron fluoride catalysis, however, yielded a diacetate as an oil with spectral indication (ir 5.72, 6.04 μ) of an *O,N*-diacetate rather than the expected **25b.** When this substance was heated with a tertiary amine (1,5-diazabicyclo[3.4.0]nonene-5) for elimination of the mesylate and the crude product (lacking sulfonyl bands in the ir) reduced with lithium aluminum hydride, *N*-ethylnortazettine (see **6**) was produced and also identified by spectral and chromatographic comparison with a sample prepared by boiling haemanthidine in ethyl iodide. These results clearly indicate that the Cannizzaro hydride transfer *had already occurred* in the hot borohydride reduction before acetylation, and this was supported by conversion of either haemanthidine or 11-oxohaemanthidine to nortazettine *via* sodium borohydride in boiling 2-propanol.

Room-temperature reduction of **24** with sodium or lithium borohydride in ether solvents (dimethoxyethane or tetrahydrofuran) did proceed to disappearance of both carbonyl bands in about 4 hr, but the product on treatment with hot alkali was transformed exclusively into 11-epihaemanthidine,[8,9] a complete reversal of stereospecificity of reduction. This surprising result may of course be rationalized by a conformational preference in **24** for a twist-boat C ring owing to the three axial groups (two of them 1,3-diaxial) present in the chair form (**19b**). Such a twist-boat conformation will offer much less hindrance to approach of hydride over the C ring, yielding the 11-epimer **25c**, but no compelling rationale is apparent for an inversion in conformational preference between protic and aprotic solvents.

Turning to acidic reduction to avoid the hydride transfer, compound **24** was treated with diborane in tetrahydrofuran, yielding monoketone **19b** at room temperature, but showing loss of both carbonyls at reflux temperatures. Treatment of the crude reduction product with alkali yielded a mixture containing both nortazettine and 11-epihaemanthidine, somewhat predominant in the latter and implying reduction to an epimeric mixture of **25a** and **25c.** In order to improve the stereospecificity, the reduction was carried out with disiamylborane, and the crude product was acetylated (acetic anhydride–boron trifluoride) to a mixture of **25b** and **25d;** this was heated with the bicyclic amidine base and reduced with lithium aluminum hydride. The same sequence of acetylation, elimination, and acetate removal by hydride has previously been tested on natural haemanthidine itself, and haemanthidine had been successfully recovered, free of nortazettine or other isomers. The sequence performed on intermediate **24** yielded (20%) racemic haemanthidine (**4a:** mp 194–196°), identical with the natural alkaloid by solution spectra (ir, nmr), mass spectrum, and the R_f values in five tlc systems. The 11-epimer was also isolated by tlc (6% yield) and similarly identified. It is important to the logic of stereospecific total synthesis to observe that, while we did not achieve controlled stereospecificity of the C-11 reduction, the identification of the two obtained epimers does not rest solely on comparison with natural material. The configuration at C-11 in the synthetic haemanthidine is independently assigned since it is the only one of the two epimers which can isomerize in base or convert to apohaemanthidine in acid.

In earlier experiments which carried the diborane reduction product through the same acetate protection–deprotection series, haemanthidine and 11-epihaemanthidine were each isolated in only 5% yield, while a third product was isolated in some 15% yield as an amorphous solid with a molecular weight of 28 units more than haemanthidine and nmr evidence for an *N*-ethyl compound similar but not identical with *N*-ethylnortazettine (above). This substance was formulated as **26b,** arising by reduction to the 11-epimer series,[9] followed by O,N-migration of the acetyl group, the final reduction taking the acetamide to an *N*-ethyl group.

Logistically, the overall synthesis consists of 30 sequential reactions, but only 19 isolations of intermediate products. The overall yield is 0.4%, an average yield of 78% per isolation step. Without the two bad steps, the Meerwein arylation of maleic acid (38%) and the final four-step conversion of **24** to haemanthidine with poor stereocontrol at C-11 (20%), the overall yield would be over 6%, pointing up the serious yield crippling of just one or two inefficient conversions in a long sequence. We sought to shorten and improve the last conversion of **24** by simply carrying out mesylate elimination on **24** or the monoketone **19b** and so obtain 11-oxohaemanthidine since we found that the latter was reducible with sodium borohydride in 2-propanol (room temperature) to a 2:1 mixture of haemanthidine and 11-epihaemanthidine, perhaps as effective stereocontrol as that used above. However, both **19b** and 11-oxohaemanthidine were destroyed in tertiary amine bases active enough for elimination.

Finally, our hopes of exploring conversion of haemanthidine to the less functionalized members of the family (**4**) were severely curtailed by the almost equal unavailability of quantities of either synthetic or natural haemanthidine. We found no evidence, however, for 3-epimerization of 11-oxohaemanthidine in methanolic acid to the presumably favored equatorial allylic methoxyl in 6-hydroxy-1-oxocrinamine. Removal of the 6-OH to produce the haemanthamine series has been achieved with dihydroapohaemanthidine *via* reduction of the 6-Cl derivative,[6] and this appears via-

ble on our intermediate **19b** as well but was not attempted.

Experimental Section

All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord (Model 137). Nuclear magnetic resonance spectra were determined using a Varian A-60A spectrometer (this spectrometer was purchased on NIH Grant No. 13183). Mass spectra were recorded on an AEI MS 12 mass spectrometer (this spectrometer was purchased on NSF Grant No. 3644). Thin-layer chromatography was carried out on silica gel HF_{254} (Brinkmann). Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y., and Amherst Microanalytical Laboratory, Amherst, Mass.

Dimethyl Piperonylidenemalonate. To 30.0 g (0.20 mol) of piperonal in 30 ml of absolute ethanol containing 2 ml of piperidine and 0.65 g of benzoic acid was added, slowly with stirring, 26.4 g (0.20 mol) of dimethyl malonate in 35 cc of absolute ethanol. After stirring for 15 hr, the solution was concentrated to half-volume at room temperature, refrigerated to crystallize, filtered, concentrated, and cooled again. The total yield of crystalline product was 34.7 g (83%), mp 68–71°, recrystallized from methanol to mp 72–73°.

Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.19; H, 4.58. Found: C, 59.20; H, 4.66.

Dimethyl α-Cyanopiperonylidenemalonate. To 5.28 g (0.02 mol) of methyl piperonylidenemalonate in 20 ml of methanol was added 1.3 g (0.02 mol) of potassium cyanide. The mixture was warmed gently on the steam bath for 45 min and allowed to cool, then added dropwise to a precooled (0°) solution of chloramine-T (4.9 g, 0.2 mol, in 30 ml of water). A gummy yellow precipitate formed, and after the solution had stood at 0° for an additional half-hour, the supernatant liquid was decanted from the yellow gum which, on trituration in cold ethanol, gave 2.85 g (49%) of methyl α-cyanopiperonylidenemalonate as yellow crystals, mp 75–85°, recrystallized from ethanol to mp 86–87°; ir ($CHCl_3$) 4.40, 5.75, 9.62 μ.

Anal. Calcd for $C_{14}H_{11}O_6N$: C, 58.13; H, 3.83; N, 4.85. Found: C, 58.31; H, 4.02; N, 5.07.

3,4-Methylenedioxyphenylmaleic Anhydride. A 6.60-g sample (0.023 mol) of dimethyl α-cyanopiperonylidenemalonate, 3.0 g (0.07 mol) of sodium hydroxide in 11.0 ml of water, and 30.0 ml of 95% ethanol were refluxed until no more ammonia was evolved (2 days). Acidification and extraction with ether led to 5.81 g of an orange-red gum. Sublimation of this gum at 150–170° (1 mm) provided 0.95 g (19%) of 3,4-methylenedioxyphenylmaleic anhydride, as orange-yellow crystals, mp 212° (lit.[14] 210–212°).

Piperonylic Acid Azide. A mixture of 227.8 g (1.67 mol) of piperonylic acid and 725 ml of thionyl chloride was refluxed until solution was complete (about 3 hr). The resulting green solution was evaporated to dryness *in vacuo*, and the residual thionyl chloride was removed by the successive addition and evaporation of three 700-ml portions of benzene. The solid acid chloride was dissolved in 1.8 l. of acetone and cooled to 0°. This solution was added slowly, with stirring and cooling, to a solution of 133 g (2.04 mol) of sodium azide in 300 ml of water. The mixture was allowed to warm to room temperature while stirring for an additional 30 min. Then 250 ml of water was added, and the mixture was left at 5° overnight. The light needles were filtered and dried giving 239.0 g (75%) of piperonylic acid azide, mp 83–84°. Two more crops of crystals were collected, 70.8 g (22%), mp 82.5–84°, and 2.46 g (<1%), mp 80–82°. The third crop was sublimed at 50° (20 μ) yielding 2.21 g of pale yellow crystals, mp 82.5–83.5°. The total yield of piperonylic acid azide was 312.0 g (97%): ir (KBr) 4.62, 5.92, 9.61 μ; nmr (CCl_4) τ 2.40 (1 H, dd, J = 2,8 Hz), 2.61 (1 H, d, J = 2 Hz), 3.21 (1 H, d, J = 8 Hz), 3.97 (2 H, s).

3,4-Methylenedioxyaniline Hydrochloride. A solution of 530 g (2.78 mol) of piperonylic acid azide in 1 l. of *tert*-amyl alcohol was refluxed for 1 hr, then cooled and evaporated to an oil which was dissolved in methanol, and 750 ml of concentrated hydrochloric acid was added slowly. The solution bubbled, and a yellow precipitate formed; this was filtered, rinsed with ether, and dried to 336 g (70%) of light yellow crystals, mp 195–205° dec. The filtrate yielded a further 109 g (23%; total, 93%) after evaporation and recrystallization from methanol–ether, mp 180–195° dec: ir (CH_2Cl_2) 3.2–3.5, 3.72, 6.32, 6.64, 7.96, 9.66 μ.

3,4-Methylenedioxphenylmaleic Anhydride. To a cooled (0–5°) slurry of 335 g (1.9 mol) of 3,4-methylenedioxyaniline hydrochloride in 1.0 l. of 6 *N* hydrochloric acid was added slowly, with stirring, a cooled (0–5°) 40% aqueous solution of sodium nitrite. After 400 ml of the solution was added, the dark foamy reaction mixture gave a positive test for excess nitrous acid. This cooled solution was then added, with stirring, to 1.35 l. of cold (0–5°) acetone containing 508 g (4.4 mol) of maleic acid and 35 g (0.35 mol) of cuprous chloride. After the solution was stirred at room temperature for 3 days, the test for diazonium ions was negative. The acetone was removed *in vacuo* and the mixture thoroughly extracted with aqueous sodium bicarbonate and ether. Acidification of the combined aqueous layers yielded a light green precipitate, and subsequent extraction with ether and evaporation yielded more diacid mixture as a light brown solid. The combined solids (243 g) were refluxed 4 hr in 1.4 l. of acetic anhydride. On cooling, the dark solution deposited 162 g (38%) of 3,4-methylenedioxyphenylmaleic anhydride, mp 225–226°: ir (KBr) 5.41, 5.62, 9.71 μ; nmr (DMSO-d_6) τ 2.20 (1 H, dd, J = 2, 8 Hz), 2.35 (1 H, d, J = 2 Hz), 2.39 (1 H, s), 2.84 (1 H, d, J = 8 Hz), 3.77 (2 H, s).

Anal. Calcd for $C_{11}H_6O_5$: C, 60.56; H, 2.77. Found: C, 60.70; H, 2.74.

Variations in the copper catalyst (metallic copper, cuprous and cupric chlorides, and mixtures) yielded only similar or lower yields. Nonaqueous media with the preformed diazonium fluoroborate salt afforded none of the desired product.

Diels–Alder Reaction to Anhydride 11. A precooled 4-l. bomb was charged with 160 g (0.73 mol) of 3,4-methylenedioxyphenylmaleic anhydride, 900 ml of chloroform, 100 ml (*ca.* 1.2 mol) of butadiene, and 4 g of hydroquinone. The bomb was then sealed, heated to 120°, charged with nitrogen to a pressure of 1000 psi, and rocked for 22 hr. After cooling to room temperature, the bomb was opened and the contents filtered. The solution was concentrated to about one-third of its volume, ether was added, and the solution was cooled overnight at −15°. The resulting pale yellow crystals were filtered and dried giving 122 g (61%) of 1-(3,4-methylenedioxyphenyl)-4-cyclohexene-1,2-dicarboxylic acid anhydride, mp 109–112°. A small sample of the anhydride was sublimed at 150° (0.15 mm) to give white crystals, mp 112–113°; ir (KBr) 5.40, 5.60, 9.62 μ.

Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.33; H, 4.51.

The corresponding diacid (**13b**), mp 204–208° (bubbling), was formed on solution of the anhydride in aqueous alkali and acidification. Diacid (0.60 g, 2.1 mmol) was esterified by refluxing 12 hr in 20 ml of methanol containing several drops of sulfuric acid. The solution was concentrated, 20 ml of water was added, and the mixture was extracted with chloroform. The chloroform extract was concentrated and passed through a short plug (2 cm) of alumina IV to remove unreacted diacid. The plug was washed with 75 ml of methanol, and the effluent was evaporated to a solid and recrystallized from methanol–water to 0.11 g of monoester **13c**, mp 183–185°. Both the diacid and the monoester were esterified by diazomethane in ether, evaporated to an oil, and crystallized from ethanol–water to crystals of the diester **13e**, mp 92–93°, identical by mixture melting point, 92–93°.

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.13; H, 5.92.

Monoester 13d. To a stirred solution of 2.0 g (0.037 mol) of sodium methoxide in 80 ml of methanol was added batchwise 10.0 g (0.037 mol) of anhydride **11**. The solution was stirred at room temperature for 30 min, then acidified with concentrated hydrochloric acid, filtered (to remove sodium chloride), concentrated *in vacuo* until crystals began to form, and left left at −15° overnight. The white crystals were filtered, washed with water, and dried, giving 9.32 g (83%) of acid ester **13d**, mp 174–178°, mixed with **13c**, mp 157–164°. A second crop of pale yellow powdery crystals weighing 223 mg (12%), mp 160–167°, was identified as a mixture of isomeric acid esters from its infrared spectrum.

Diazomethane esterification as above yielded crystals of diester **13e**, mp 91–93°, mmp 92–93°. Partial saponification of the diester (1.67 g, 5.25 mmol) was carried out in 5 ml of 1.56 *N* potassium hydroxide diluted with 5 ml of methanol; the solution was refluxed until slightly more than 1 equiv of base was consumed (1.5 hr). The solution was concentrated, water was added (10 ml), and the solution was washed with chloroform. Acidification of the aqueous

base layer, followed by chloroform extraction and evaporation, yielded 0.90 g of white crystals, mp 168–174°, recrystallized from methanol–water to mp 175–178°, mmp (with **13d** above) 174–178°.

Lactam Ester 15. Fifty milliliters of oxalyl chloride was added to 20.1 g (0.065 mol) of acid ester **13d** and stirred at room temperature until solution was complete (about 1 hr). The excess oxalyl chloride was removed *in vacuo* and further stripped by two evaporations with benzene, leaving a white solid which was dissolved in 200 ml of acetone, cooled, and added with cooling and stirring to 8.88 g (0.14 mol) of sodium azide in a minimum of water. The reaction mixture was allowed to come to room temperature, water was added, and the white gum that formed was extracted into ether. The colorless oil that was left after evaporation of the ether was dissolved in toluene and refluxed for 2 hr. The toluene was removed *in vacuo* leaving 19.5 g (98% crude) of an oil whose infrared spectrum indicated no unrearranged acid azide. No attempt was made to purify the isocyanate further.

To the crude isocyanate was added about 50 ml of polyphosphoric acid, and the thick syrup was stirred manually for 30 min. As the reaction progressed, the mixture darkened from pink to red-brown, became more viscous, and became warm. Water was then added to the syrup, which slowly dissolved and became light colored as a light yellow precipitate formed. This was filtered, washed well with water, and dried, giving 16.19 g (81.3%) of the lactam ester **15,** mp 275–278°. Recrystallization from chloroform:ether gave white crystals, mp 279–281°: ir (KBr) 5.78, 5.98, 9.64 μ; nmr (DMSO-d_6) τ 2.66 (1 H, s), 2.98 (1 H, s), 3.87 (2 H, s), 4.27 (2 H, m), 6.81 (3 H, s).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02. Found: C, 63.53; H, 5.36.

Lactam Acid 16. A mixture of 1.02 g (3.4 mmol) of lactam ester (**15**), 10 ml of methanol, and 10 ml of 40% aqueous potassium hydroxide solution was refluxed gently for 2 hr, after which time all the solid had dissolved. An additional 12 ml of water was added to the orange solution and the solution refluxed for another hour. Upon cooling to room temperature, the solution yielded white needle crystals. These were filtered and dried giving 0.904 g (82%) of the acid salt. The mother liquor yielded a second crop of white crystals (151 mg, 14%). The remaining filtrate was cooled overnight at −15°, and a third crop of pale yellow crystals was collected, providing an additional 50 mg (4%) of the acid salt: ir (KBr) 6.00, 6.29, 6.82, 9.60 μ.

The acid **16** was prepared by slow acidification of an aqueous solution of the salt. Cooling and filtering yielded white crystals, mp 250–255° dec.

Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.88. Found: C, 62.55; H, 4.70; N, 5.07.

Iodolactone 20a. A mixture of 11.86 g (36.5 mmol) of lactam acid salt, 9.55 g (37.6 mmol) of iodine, and 6.17 g (37.2 mmol) of potassium iodide in 600 ml of saturated sodium bicarbonate solution was stirred at room temperature for 4 hr. The excess iodine was destroyed with 60 ml of 5% sodium thiosulfate solution, and the mixture was then acidified with 480 ml of 1 *N* hydrochloric acid and 30 ml of 6 *N* hydrochloric acid. The resulting yellow precipitate was filtered, rinsed with water, and dried, giving 13.46 g (92%) of the iodolactone, mp 268–270°: ir (KBr) 5.58, 5.97, 9.62 μ.

Anal. Calcd for $C_{15}H_{12}NO_5I$: C, 43.59; H, 2.93; I, 30.71. Found: C, 43.48; H, 2.78; I, 31.0.

Methoxylactone 20b. To 15.0 g (36.4 mmol of iodolactone **20a** were added 365 ml of 0.1 *N* sodium hydroxide solution and 36.5 ml of 1 *N* sodium hydroxide solution, and the resulting mixture was heated until most of the solid had dissolved (5 hr). The solution was then filtered, giving back 209 mg of iodolactone, and then left at −15° for 18 hr. The ice was allowed to melt, and the tiny crystals that remained were filtered and dried, providing 9.42 g (80%) of the epoxy acid salt **21:** ir (KBr) 6.06, 6.22, 9.68 μ.

The epoxy acid salt **21** was slurried in 300 ml of absolute methanol; boron trifluoride was bubbled in slowly for 5 min, and the mixture was stirred for 24 hr. The white crystals were filtered, rinsed with water, and dried, giving 6.34 g (69%) of the methoxylactone, mp 274–275°, recrystallized from methanol to mp 278–279°: ir (KBr) 5.66, 5.97, 9.66 μ; mass spectrum *m/e* 317, 273, 258, 241, 215, 202.

Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.55; H, 4.77. Found: C, 60.71; H, 4.76.

Hydroxy Acid Salt from Methoxylactone 20b. To a suspension of 4.14 g (13.0 mmol) of methoxy lactone **20b** in 450 ml of methanol was added 14.3 ml of 1 *N* sodium hydroxide solution (a 10% excess), and the mixture was boiled for 1 hr, after which time all the solid had dissolved. The solvent was removed *in vacuo* leaving a thick syrup which was taken up in hot methanol, triturated carefully with ether, and cooled at −15° overnight. The solid hydroxy acid salt was filtered and dried, giving 2.79 g (60%). A second crop yielded 1.64 g (35%) of the acid salt: ir (KBr) 6.00, 6.34, 9.64 μ.

***p*-Bromophenacyl Ester Mesylate 22a.** A solution of 3.73 g (10.4 mmol) of the hydroxy acid salt and 3.43 g (12.3 mmol) of *p*-bromophenacyl bromide in 230 ml of dimethylformamide was stirred at room temperature for 16 hr. The dimethylformamide was then removed *in vacuo* leaving a yellow slightly opaque syrup, which was taken up in methylene chloride and filtered to remove sodium bromide. The solution was evaporated leaving a clear yellow oil which when taken up in 100 ml of 1:1 benzene:methylene chloride, triturated with petroleum ether and cooled to −15° yielded 4.73 g (85%) of a white solid, the *p*-bromophenacyl ester, mp 151–157°. A second crop yielded 0.44 g (8%) of the ester: ir (KBr) 5.78, 5.91, 6.06, 9.69 μ.

A solution of 2.85 g (5.08 mmol) of the *p*-bromophenacyl ester in 100 ml of dry pyridine was cooled to −20°, 5 ml (64 mmol) of methanesulfonyl chloride was added dropwise, and the reaction mixture was stirred at −20° for 3 hr. The opaque yellow solution was then added to 100 ml of methylene chloride and washed with sodium bicarbonate solution, then with water. The organic layer was then separated, dried (Na_2SO_4), and evaporated to 3.30 g of a yellow oil which on solution in hot 95% ethanol and cooling yielded 1.61 g (49%) of the mesylate ester **22a** as white crystals, mp 227–230°, recrystallized from ethanol to mp 232–233°. A second crop weighing 0.19 g (6%), mp 224–226°, was also collected. Upon evaporation of most of the ethanol, 0.19 g (11%) of methoxylactone **20b** crystallized out. Ir (KBr) 5.72, 5.91, 5.96, 7.43, 8.52, 9.65 μ; nmr (DMSO-d_6) τ 2.32 (4 H, s), 2.70 (1 H, s), 2.93 (1 H, s), 3.85 (2 H, s), 4.78 (2 H, m), 5.04 (1 H, m), 6.64 (s), 6.72 (total 5 H, s).

Anal. Calcd for $C_{25}H_{24}NO_{10}BrS$: C, 49.19; H, 3.96; Br, 13.09. Found: C, 49.08; H, 4.06; Br, 12.88.

Acid Chloride 22c. Mesylate acid **22b** was prepared by stirring a mixture of 433 mg (0.71 mmol) of mesylate ester **22a** and one powdered potassium hydroxide pellet in 15 ml of tetrahydrofuran at room temperature for 12 hr. The dark brown mixture was then acidified with seven drops of 6 *N* hydrochloric acid, with stirring and cooling, and the precipitated inorganic salts were filtered off the deep yellow solution. The solvent was evaporated *in vacuo* leaving 479 mg of an orange glass.

The crude acid mixture was taken up in 15 ml of thionyl chloride and stirred at room temperature for 21 hr. After evaporation of the thionyl chloride, 525 mg of an oil remained. This oil was dissolved in methylene chloride, and ether was added to the cloud point. Cooling produced crystals which were filtered and dried, giving 223 mg (76%) of the acid chloride, mp 191–193°. A second crop provided 36 mg (12%), mp 190–193°, and a third crop gave 13 mg (4%), mp 188–191°: ir (KBr) 5.58, 5.98, 7.52, 8.49, 9.62 μ; mass spectrum *m/e* 431, 368, 272, 240, 202.

Diazo Ketone 22d. A mixture of 258 mg (0.60 mmol) of acid chloride **22c** and 39 mg of potassium carbonate in 25 ml of dioxane (distilled from lithium aluminum hydride) was cooled until the dioxane just began to freeze. Then diazomethane was distilled into the mixture as it gradually warmed to room temperature. The flask was then stoppered with a rubber septum. After a 17-hr period of stirring at room temperature in a closed system, no acid chloride could be detected by tlc. The mixture was filtered, evaporated to 346 mg of a yellow oil, ir 4.72 μ, which crystallized from cold methylene chloride–ether to 109 mg (42%) of the diazo ketone, mp 171.5–173.5°. Two more crops were collected, 77 mg (30%), mp 165–171°, and 57 mg (22%), mp 155–165°. The combined crystals were recrystallized from methanol to mp 179–180° but gave unsatisfactory analyses: ir (KBr) 4.72, 6.01, 7.49, 8.54, 9.65 μ.

Cyclization to the Ketone Quasi-Amide 24. A 184-mg (0.42 mmol) sample of recrystallized diazo ketone **22d** (mp 178–180°) was suspended in 40 ml of methylene chloride. Into the suspension was bubbled dry hydrogen chloride for 30 sec. Effervescence was observed, and the solution became clear. The solution was left stir-

ring at room temperature for 30 min and then given one quick wash with saturated sodium bicarbonate solution, separated, and dried (Na_2SO_4), and the solvent was evaporated, leaving 201 mg of a yellow oil. Preparative tlc provided 95 mg (55%) of the cyclized product **24,** recrystallized from methylene chloride–ether to 81 mg of crystals, mp 193–194°: ir (CH_2Cl_2) 5.68, 5.85, 7.49, 8.51, 9.64 μ; mass spectrum *m/e* 409, 381, 286, 271, 255, 240, 225.

Anal. Calcd for $C_{18}H_{19}NO_8S$: C, 52.83; H, 4.65. Found: C, 52.51; H, 4.74.

A slurry of **24** (10 mg) and 16 mg of sodium borohydride in 1 ml of 2-propanol was stirred overnight and extracted with water–methylene chloride yielding an oil lacking the 5.85-μ ir band.

Nortazettine (6). A 190-mg (0.47 mmol) sample of ketone **24** and 332 mg of sodium borohydride were taken up in 20 ml of 2-propanol and refluxed for 2 hr. The solvent was evaporated, the residue partitioned between water and methylene chloride, and the aqueous phase continuously extracted with methylene chloride overnight. Evaporation of the methylene chloride gave 152 mg (80%) of an oil, the infrared spectrum of which indicated that both carbonyls had been reduced. The oil was taken up in methylene chloride, triturated with petroleum ether and cooled, giving 122 mg of a white solid, mp 130–140°: ir (CH_2Cl_2) 6.73, 7.41, 8.51, 9.62 μ; nmr ($CDCl_3$) τ 237 (2 H, s), 3.77 (2 H, s), 4.93 (2–3 H, br), 6.15 (3.4 H, br), 6.45 (3 H, s), 6.72 (3 H, s).

A 17-mg sample was taken up in 1.5 ml of methanol and 1.5 ml of 40% potassium solution and refluxed 5 hr. This was evaporated, 3 ml of water was added, and the aqueous phase was extracted three times with methylene chloride. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated leaving 6 mg of an oil which was identified as nortazettine by comparison with a sample prepared similarly from haemanthidine,[23] by coincident ir and nmr spectra and tlc behavior in three solvent systems.

Hydride Reductions of 24. Small samples of **24** were reduced at room temperature with 1–3 times the weight of hydride, and the product was examined for reduction of one or two carbonyls by ir as above. If both were reduced, the product was further treated with base as above and compared with nortazettine and 11-epihaemanthidine[8] by ir and tlc. A selection of key results appears in Table I.

Table I. Hydride Reductions of **24**

Hydride	Solvent	Time, hr	Reduction	Base product
$NaBH_4$	*i*-PrOH	72	One CO	
$NaBH_4$	DME	67	Both	11-epi H
$LiBH_4$	*i*-PrOH	48	One	
$LiBH_4$	THF	4	Both	11-epi H
$LiAlH_4$	THF	4	Both	Many products (tlc)
$NaBH_4$	THF (hot)	2	Both	Nortazettine

Haemanthidine (4a). A mixture of 50 mg (0.12 mmol) of **24** and 0.5 ml of tetrahydrofuran–borane solution was refluxed for 3 hr and cooled, water was added, and the aqueous phase was extracted three times with methylene chloride to give 44 mg of an oil: ir (CH_2Cl_2) 6.73, 7.45, 8.52, 9.62 μ. The oil was dissolved in 4.5 ml of acetic anhydride and cooled to 0°; 1.5 ml of boron trifluoride etherate was added and the solution allowed to stand at 5° for 13 hr, then poured into water, stirred at room temperature for 30 min, and extracted with methylene chloride. This solution was washed with saturated sodium bicarbonate solution and once with water, dried (Na_2SO_4), and evaporated to 44 mg of an oil: ir (CH_2Cl_2) 5.68 (shoulder), 5.73, 6.73, 7.32–7.50 (br), 8.49, 9.60 μ. The oil was dissolved in 14 drops of 1,5-diazabicyclo[3.4.0]nonene-5 and heated to 110° for 3 hr. The resulting dark-brown liquid was taken up in methylene chloride, extracted two times with water to remove excess base, dried (Na_2SO_4), and evaporated to 104 mg of a brown oil: ir (CH_2Cl_2) 5.73, 9.63 μ. This oil was dissolved in 3 ml of dry tetrahydrofuran, and the solution was cooled to 0°. A few grains of lithium aluminum hydride were added, and the mixture was stirred at 0° for 2 hr. Water was added cautiously to destroy the excess lithium aluminum hydride, and the solvent was evaporated. Water was added to the residue and extracted three times with methylene chloride giving, after drying (Na_2SO_4) and evaporation, 10 mg of an oil. Preparative tlc afforded three components: (a) 6 mg, mass spectrum *m/e* 345, 284, 263, 256, 224, 209; (b) 2 mg, mass spectrum *m/e* 317, 302, 299, 284, 268, 258, 254, 240, 227, 209, 200, essentially identical with the mass spectrum of haemanthidine; (c) 2 mg, mass spectrum *m/e* 317, 302, 299, 284, 268, 256, 244, 233, 201, essentially identical with that of 11-epihaemanthidine,[22] as was the tlc behavior.

Improved preparation: A 190-mg sample of ketone **24** was refluxed for 6 hr in 2 ml of disiamylborane solution prepared from 286 mg of 2-methyl-2-butene and 2 ml of 1 *M* tetrahydrofuran–borane solution. The reaction was worked up as described above for the diborane reaction. Likewise, the acetylation, elimination, and final lithium aluminum hydride reduction steps were carried out in the same way as described above. Preparative tlc separation gave 29 mg (20%) of haemanthidine, isolated as an amorphous solid. Recrystallization from acetone gave crystalline *d,l*-haemanthidine, mp 193.5–195.5°. Only 8 mg of the 11-epimer was isolated, and 40 mg of other material representing more than one band, which still displayed weak sulfonyl absorption but was not treated further. The nmr and ir spectra ($CHCl_3$) were coincident with those of natural haemanthidine as were the R_f values in five tlc solvent systems (also identical with component b above). The same elimination and lithium aluminum hydride treatment of haemanthidine diacetate led largely to recovered haemanthidine.

***N*-Ethylnortazettine.** When the reduction of **24** was carried out with sodium borohydride in hot 2-propanol as in the preparation of nortazettine above and followed without isolation by the acetylation described for haemanthidine above, an oil was obtained: ir 5.72, 6.04, 7.33, 8.17, 8.50, 9.63 μ. This oil was subjected to elimination and lithium aluminum hydride treatment as for haemanthidine (above). The product exhibited the same ir and mass spectra and tlc behavior as a sample of *N*-ethylnortazettine, prepared by heating haemanthidine in ethyl iodide, but was different from component a in the haemanthidine preparation which has the same molecular weight.

Diazo Ketone 17. To 964 mg (3.36 mmol) of the acid **16** was added 15.0 ml of thionyl chloride, and the mixture was stirred at room temperature for 20 hr. The excess thionyl chloride was then removed *in vacuo* at room temperature utilizing a 5.0-ml portion of dry benzene to remove the last traces. The solid acid chloride was added batchwise to excess diazomethane (*ca.* 15 mmol in 50 ml of anhydrous ether and 100 ml dioxane dry at 0° over a period of 0.5 hr. Another 50 ml of dry dioxane was used to rinse out the flask containing the acid chloride. After the addition was completed, a total of 500 mg of solid potassium carbonate was added, with stirring, over a period of 6 hr under a drying tube. The reaction mixture was then refrigerated for 16 hr, allowed to warm to room temperature, and kept there for an additional 24 hr.

Filtration and concentration *in vacuo* provided a yellow solid which was dissolved in chloroform, filtered, and concentrated to an oil that crystallized upon trituration with ether. Cooling followed by filtration and washing with cold ether gave 1.09 g (96%) of product, mp 161–162°, recrystallized from methanol to white crystals, mp 161–162°: ir (Nujol) 3.10, 4.67, 5.93, 9.65 μ.

Anal. Calcd for $C_{16}H_{13}O_4N_3$: C, 61.73; H, 4.21. Found: C, 61.64; H, 4.33.

6,11-Dioxocrinene-2 (18a). Dry hydrogen chloride was bubbled into a solution of 440 mg (1.42 mmol) of **17** in 100 ml of methylene chloride until the evolution of nitrogen was observed. The solution was then allowed to stand at room temperature until all bubbling ceased (about 0.5 hr). A rapid washing with cold aqueous sodium bicarbonate solution followed by thorough drying over anhydrous magnesium sulfate gave, upon concentration and addition of ether, 333 mg (82%) of crude dioxocrinene, mp 211–219°, recrystallized from methylene chloride:ether (1:1) to mp 217–219°: ir (Nujol) 5.68, 5.85, 9.62 μ; uv (CH_3CN) 238 (4.33), 273 (3.83), 315 (3.66) nm; nmr ($CDCl_3$) τ 2.55 (1 H, s), 3.15 (1 H, s), 3.82 (2 H, s), 4.28 (2 H, br s).

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63. Found: C, 67.72; H, 4.85.

Reduction with sodium borohydride in methanol at room temperature yielded a partly crystalline oil **18b** showing two spots of similar R_f and intensity in tlc and no carbonyl in the ir spectrum.

6-Hydroxy-11-oxocrinene-2 (18c). A solution of 105 mg (0.37 mmol) of dioxocrinene (**18a**) in dry tetrahydrofuran was cooled to −20°, sodium borohydride (107 mg, 2.8 mmol) was added, and the solution was stirred at −20° for 1 hr. The excess hydride was de-

composed by adding solid acetic acid (1 g), then 2 ml of 3 *N* hydrochloric acid (cooled to −20°), and the solution was stirred at −20° for 0.5 hr more. Hydrochloric acid (5 ml of 2 *N*) was added; the mixture was stirred at room temperature (0.5 hr), and then evaporated, and the residue was dissolved in water, made strongly basic with potassium hydroxide, and extracted with methylene chloride. Drying and evaporating yielded 90 mg of crude solid **18c**, recrystallized from methanol–chloroform to mp 247–248°: uv (MeOH) 213, 251, 295 nm; ir (KBr) 2.92, 5.69, 9.63 μ.

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 67.36; H, 5.30. Found: C, 67.31; H, 5.47.

Epoxidation of 18c. Freshly recrystallized silver acetate (31 mg, 0.18 mmol) and 6-hydroxy-11-oxocrinene-2 (52 mg, 0.18 mmol) were dissolved in 4 ml of glacial acetic acid and protected from light and moisture. Iodine (48 mg, 0.19 mmol) in 4 ml of glacial acetic acid was slowly added as color disappeared and precipitate appeared. The slurry was stirred 40 min and filtered through Celite, and excess iodine was discharged with aqueous sodium thiosulfate. The solution was evaporated to a gum which was dissolved in methanol, and methanolic potassium hydroxide was added. After 45 min, water was added, and extraction with methylene chloride afforded 46 mg, crystallized with methanol to mp ~260° dec: mass spectrum *m/e* 301; ir (KBr) 2.91, 5.70, 9.62 μ.

Treatment of the epoxide at 0° with dry boron trifluoride in methanol under nitrogen for 2 hr, followed by partition between aqueous sodium carbonate and chloroform, yielded a semisolid showing two close and equal spots on tlc and nmr ($CDCl_3$) τ 2.38 (2 H, s), 3.80 (2 H, s), 6.44 (3 H, s), 6.51 (3 H, s). A small sample from several tlc separations recrystallized from methanol–chloroform to mp 228–232°; mass spectrum *m/e* 333.

Acknowledgment. We acknowledge research support for much of this work from NIH Grant 10715.

References and Notes

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(16) Epimerization at the tertiary site in these derivations was ruled out since all acids gave the same diester on diazomethane treatment, and all were easily reconverted to the anhydride **11** on sublimation. Hence the difference in **13c** and **13d** is structural, not stereochemical. This lack of epimerization is also (negative) evidence for the correctness of the stereochemical assignment in the rest of the synthetic sequence in Chart I.

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(18) The tosylate of the hindered C-2 hydroxyl could not be formed to test this speculation. The result is consistent with the view that in mesylate formation the active intermediate sulfene ($CH_2{=}SO_2$) is formed first and is the actual sulfonating agent,[19] impossible with the toluenesulfonyl derivative. Analogously, treatment of the mesylate **22a** with strong base may also create the sulfene, releasing the oxygen for lactonization to **20b**. The alkali saponification–elimination also yielded some methoxyl-actone.

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(20) Cyclization of both diazo ketones **17** and **22d** was successful with hydrogen chloride but not with boron fluoride catalysis, which implies the necessary intermediacy of a chloromethyl ketone followed by internal displacement.

(21) Reduction with lithium aluminum hydride led to a complex mixture with spectral indication of considerable loss of sulfonyl bands, as expected.

(22) A generous sample of nataline was provided by Professor Frank Warren, Department of Chemistry, University of Cape Town, South Africa. This substance was shown to be an approximately 1:1 mixture of haemanthidine and its 3-epimer, 6-hydroxycrinamine (**4a**), separable by thin-layer chromatography. From this sample were prepared 11-oxohaemanthidine[8] and by hydride reduction, 11-epihaemanthidine,[8,9] for comparison samples, as well as nortazettine.[23]

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