Constituents of *Nauclea diderrichii*. Part VII. Synthesis of naucleđerine, naucleonine, and naucleonidine; spectroscopic evidence for the structures of 3α-dihydrocadambine and two other constituents

STEWART MCLEAN, GARY I. DMITRIENKO, AND AKOS SZAKOLCAI
Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1

Received October 23, 1975

STEWART MCLEAN, GARY I. DMITRIENKO, and AKOS SZAKOLCAI. Can. J. Chem. **54**, 1262 (1976).

Evidence is advanced concerning the structures of six *N. diderrichii* alkaloids, based on synthetic and spectroscopic studies. The synthesis of naucleđerine, **2**, provides support for the structural assignment made earlier. Synthesis has shown that the structures previously assigned to the alkaloids designated ND-305B and ND-363C are incorrect; this, however, has led to revised structures (**19** and **20**) for these alkaloids, now named naucleonine and naucleonidine, respectively, and these have been established by synthesis. Based on this study and an examination of data obtained previously, a tentative proposal is made for the structure **21** of another constituent of the plant, designated ND-363B. Spectroscopic studies have allowed a structure **22** to be advanced for the glycosidic alkaloid, which was shown to be identical with the alkaloid 3α-dihydrocadambine obtained by Brown and Fraser. Based on this study and a reexamination of data reported previously, structure **25** is tentatively proposed for another constituent of the plant, designated ND-370.

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On présente des données, basées sur des études de synthèse et de spectroscopie, concernant la structure de six alcaloïdes *N. diderrichii*. La synthèse de la nauclédérine, **2**, fournit une preuve supplémentaire pour l'attribution de structure proposée antérieurement. On a démontré, par synthèse, que les structures proposées antérieurement pour les alcaloïdes ND-305B et ND-363C ne sont pas correctes. Nos études ont toutefois permis d'attribuer les structures revisées (**19** et **20**) à ces alcaloïdes qui sont maintenant nommés respectivement naucléonine et naucléonidine; ces structures ont maintenant été établies par synthèse. En se basant sur l'étude présente et en réexaminant les données obtenues antérieurement, une structure non-définitive **21** est proposée pour le constituant ND-363B de la plante. Des études spectroscopiques ont permis de proposer la structure **22** pour l'alcaloïde glycosidique; on a montré que cet alcaloïde est identique avec l'alcaloïde 3α dihydrocadambine obtenu par Brown et Fraser. En se basant sur l'étude actuelle et à l'aide d'un réexamen des données obtenues antérieurement, on propose, d'une façon non-définitive, la structure **25** pour le constituant ND-370 de la plante.

[Traduit par le journal]

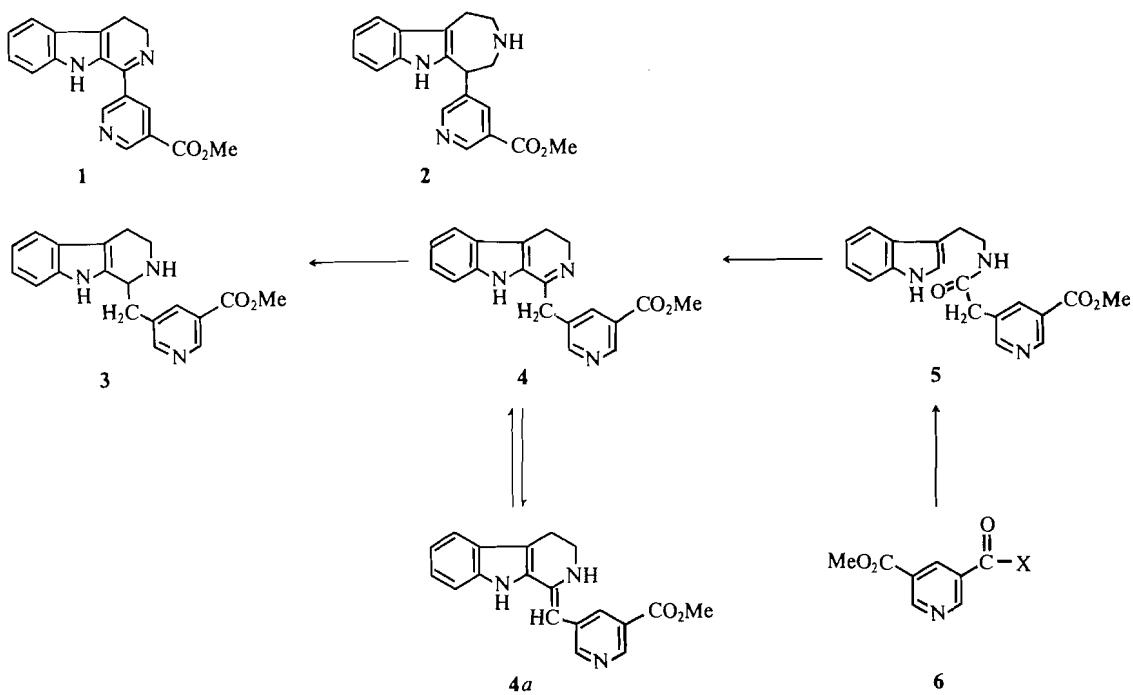
We have described the isolation of constituents of *Nauclea diderrichii* which, for convenience, we have placed in four categories (1). The structures of all of the members of the first two groups, the simple β-carbolines and the simple pyridines were established with confidence (1*a*). In the third group, the indole-pyridine alkaloids, only naucledine, **1**, was assigned a structure unequivocally, but provisional structures were advanced for other members of the group with varying degrees of confidence (1*b*). Structural assignments to the members of the fourth group, miscellaneous substances, were at best tentative (1*c*). More recently we have published preliminary communications in which we make firm structural assignments to several members of the third and fourth groups (2). We now provide details of these latter assignments and also describe progress in the elucidation of the structures of several other constituents of this plant.

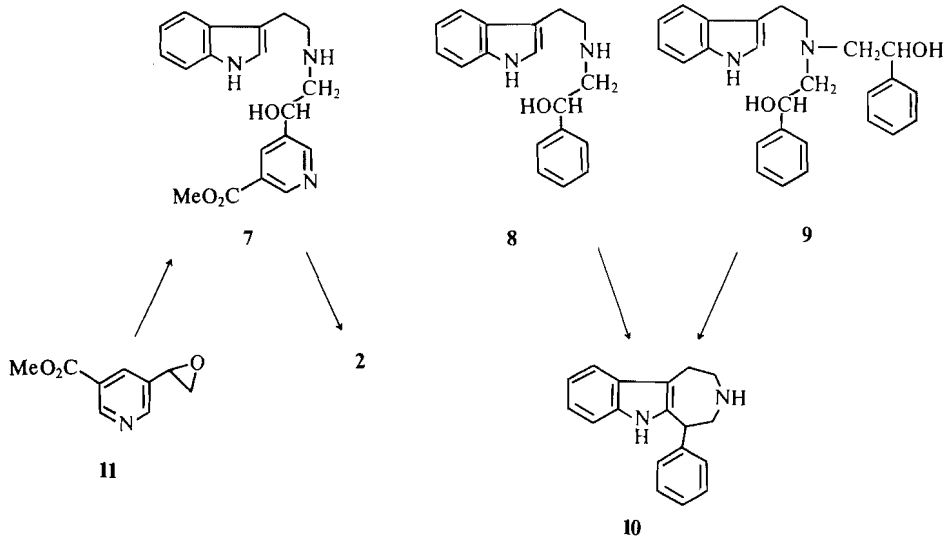
Because of the small amounts of material available from natural sources (1*a*), it has been necessary throughout this study to resort to total synthesis to test and substantiate the structural assignments based on spectroscopic studies. The structure of the first indole-pyridine alkaloid, naucledine, **1**, was established in this way (1*b*), and, of the other members of this group, naucleđerine appeared to be the best candidate for a synthetic attack. The favored structure for naucleđerine was the azepinoindole **2**, but a small

number of alternative structures remained possible though unlikely since each was difficult to reconcile with at least one piece of spectroscopic data. One of these, the picolyltetrahydro-β-carboline **3**, which was considered unlikely on the basis of the fragmentation pattern in the mass spectrum of the alkaloid, was disposed of when it was synthesized and shown to be different from the alkaloid. (The mass spectrum of **3** was that expected for the structure.) The synthesis of **3** was accomplished by Bischler–Napieralski cyclization of the amide **5** and sodium borohydride reduction of the dihydro-β-carboline product. The amide **5** was prepared from the dinicotinic acid derivative **6** (X = Cl) (1*a*) by an Arndt–Eistert sequence in which the intermediate diazo ketone **6** (X = CHN_2) was allowed to react with tryptamine in the presence of silver oxide. An interesting feature of the dihydro-β-carboline intermediate is that its nmr spectrum shows that the imine form **4** exists in dynamic equilibrium with the enamine **4***a*; the proton signals indicate that both tautomeric forms are present in substantial amounts in the solution and the addition of D_2O removes all of the signals associated with the mobile hydrogens.

A route to the favored structure, **2**, by acid-catalyzed cyclization of the amino alcohol **7** could be seen but it was considered advisable to explore this approach by attempting the cyclization of the phenyl analog **8**, which seemed to be more readily accessible. This intermediate could, indeed, be prepared by the reaction of tryptamine with styrene bromohydrin or the epoxide derived from it, but under all of the reaction conditions used, significant amounts of the bis product **9** were obtained; attempts to prevent over-reaction left unchanged tryptamine and presented subsequent problems with purification of the product, and the best practical course was found to be the quantitative conversion of tryptamine to **9** with styrene oxide. A route to **8** alone by the reaction of tryptamine with *O*-acetylmandelyl chloride followed by hydrolysis of the ester and reduction of the amide was developed, but this was of little advantage since it was found that polyphosphoric acid converted both **8** and **9** to **10**, the phenyl analog of **2**, with about the same efficiency; it is probable that **9** produced the *N*-substituted derivative of **10**, which underwent dehydration and hydrolysis under the reaction conditions (3). The product **10** was identical with material assigned this structure by Freter (4), and obtained by a different route.

The epoxide precursor, **11**, required for the synthesis of **2** itself was most conveniently pre-





pared from the bromohydrin obtained by treatment of the diazo ketone **6** (X = CHN_2) with hydrobromic acid followed by borohydride reduction of the resulting bromo ketone. A small amount of the epoxide itself was formed in this reduction, but the bulk of the product was bromohydrin which was converted to epoxide by treatment with sodium hydride under mild conditions. The epoxide was obtained crystalline, mp 63.5–64.5 °C, by sublimation (60 °C/0.05 torr) and was stable up to this temperature. (In contrast, the epoxide of 4-vinylpyridine has been described (5) as an unstable liquid.) As in the model series, problems with bis alkylation were found when tryptamine was treated with epoxide **11**, but in this case conditions were found in which acceptable yields of **7** could be isolated, provided that the reaction was carried out batchwise with small amounts of reactants. After numerous attempts, conditions were found in which **7** was cyclized to **2**, albeit in only 5.4% yield. The structural identity of **2** and natural naucleferine was judged from their spectroscopic (ir, uv, nmr, and ms) and tlc characteristics. The natural material melted over a wide range (102–124 °C), and comment has been made about this previously (1*b*); the range observed for the synthetic material (94–108 °C) was similar, but did not serve as a good criterion of identity. Microanalytical values indicated that synthetic **2** retained a molecule of solvent of crystallization, but completely satisfactory and reproducible results could not be obtained with the small amount of material available and, as with natural naucleferine, the best proof of constitution came from a determination of the masses of the parent ion and certain fragment ions in a high resolution mass spectrum.

In an attempt to improve the yield in the cyclization step, the *N*,*O*-diacetyl derivative of **7** was prepared with the intention of selectively hydrolyzing the ester function and leaving the nitrogen protected during the treatment with polyphosphoric acid. A feature of interest in this diacetyl derivative and the corresponding derivatives in the model series is that the nmr spectrum shows two signals for the *N*-acetyl protons, indicative of the existence of two relatively stable rotamers. However, the *N*-acetyl group proved to be unusually susceptible to acid hydrolysis and, by using the nmr spectrometer to monitor the course of the reaction, it could be seen that the hydrolysis of the original *O*-acetyl group was followed by a rapid $N \rightarrow O$-acetyl migration and then further hydrolysis. It seemed most improbable, therefore, that the *N*-acetyl group would provide any protection in the polyphosphoric acid treatment. The *N*-tosyl derivative was also prepared and subjected to cyclization in polyphosphoric acid, but without any improvement in yield.

The isolation of naucleferine, even in small yield, provides strong support for the proposed structure **2**. It is recognized, however, that this sequence does not quite reach the level of a completely unequivocal proof of structure, since

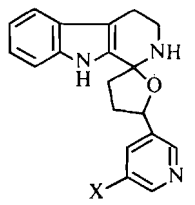
the mechanism of the acid-catalyzed cyclization step has not been established. The nature of the electrophilic centre generated in the reaction has not been established, and the possibility exists that an aziridinium intermediate could be formed and lead to rearranged product. In any case, the electrophilic centre may well attack the β-position of the indole generating a six-membered ring, with subsequent Plancher rearrangement of the spiroindolenine providing the azepinoindole (6). Even if this were so, migration of the picolyl substituent to form **2** can be expected rather than the alternative rearrangement. Furthermore, the formation of **10** from **8** and from the precursor used by Freter (4) buttresses its structural assignment and provides firm support for the assignment of **2** to nauclederine, which strongly resembles **10** spectroscopically.

A further member of the indole-pyridine group of alkaloids was the substance referred to by its laboratory designation ND-363C and tentatively assigned structure **12** (X = CO_2Me) as a working hypothesis (1*b*). It was recognized that the sample consisted of a pair of equilibratible epimers and it was postulated that opening and closing the carbinolamine ether (*cf.* **13**) provided a route for the epimerization. However, two pieces of spectroscopic data could not readily be accommodated by this hypothesis: the presence in the nmr spectrum of a τ 8.22 peak, readily removed by addition of D_2O, and the occurrence of an $M - CH_3$ ion as the base peak in the mass spectrum. Another substance, ND-305B, was closely similar in its behavior and was considered to be the decarbomethoxy analog **12** (X = H).

As a test of the structural hypothesis, synthesis of the ring-opened tautomers **13** was undertaken, and the most readily available model was **13** (R = H). γ-Butyrolactone **15** (R = H) reacted smoothly with tryptamine to form the amide **14** (R = H), which was protected as its *O*-acetyl derivative and subjected to Bischler–Napieralski cyclization. Careful hydrolysis of the *O*-acetyl group led to **13** (R = H) which was isolated as a waxy solid. However, this material showed spectroscopic characteristics appropriate for the ring-opened imine form and showed no tendency to cyclize to the carbinolamine ether; in particular, the nmr spectrum showed no evidence for tautomerism and the uv spectrum was that of a typical dihydro-β-carboline in acidic, neutral, and basic media. The same sequence was carried out with the phenylbutyrolactone **15** (R = Ph) and the pyridyl analog **15** (R = 3-pyridyl) which was prepared from ethyl nicotinate by a routine synthetic sequence. In both cases the product existed in the imine form **13**, and it was clear that the equilibrium was not shifted to favor the ring-closed tautomer by an effect associated with either the bulk of the substituent or a special characteristic of the pyridyl group. Clearly the original structural hypothesis was incorrect, and, in particular, **13** (R = 3-pyridyl) was not identical with ND-305B nor did it lead to it.

Because these observations raised questions regarding the proposed tautomerism, the imminium salt **17** (R = H) was prepared by the reaction of harmalan, **16**, with 2-bromoethanol, and when this was treated with aqueous base, it spontaneously formed the ring-closed product **18** (R = H). Two spectroscopic properties of this material were of commanding interest: the mass spectrum showed an $M - CH_3$ base peak and the nmr spectrum showed a three-proton singlet at τ 8.28 which rapidly disappeared when the sample was shaken with D_2O. Clearly the latter observation indicates that some of the enamine tautomer is in equilibrium with the carbinolamine ether. Furthermore, when harmalan was treated with styrene oxide, **18** (R = Ph) was formed directly and this material showed, in addition to the two spectroscopic features just mentioned, the 'doubling' of the nmr spectrum that had been associated in the case of the alkaloids with the existence of a pair of epimers differing in stereochemistry at the point of ring-closure. An explanation for the problematic spectroscopic observations for the alkaloids was immediately apparent, and the true structures of ND-363C and ND-305B were revealed (2*b*).

The obvious synthetic precursor to ND-363C was the epoxide **11** which was already available (see above), and reaction of this with harmalan in refluxing chloroform led to the isolation of a glassy solid in 46% yield which showed tlc behavior identical to that of natural ND-363C. This product did not crystallize, nor could a crystalline derivative be prepared from it, but a sample of the synthetic material that was carefully purified by chromatography gave a satisfactory analysis for the expected formula $C_{21}H_{21}N_3O_3$. The spectroscopic properties, including the p*H* dependence of the uv spectra, of



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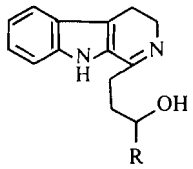

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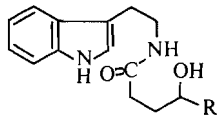

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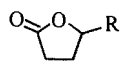

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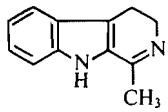

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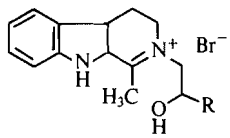

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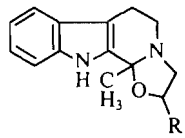

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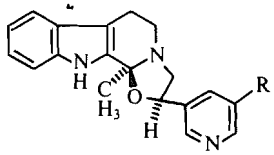
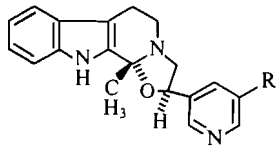




19*a* α-Naucleonine R = H
20*a* α-Naucleonidine R = CO_2Me

19*b* β-Naucleonine
20*b* β-Naucleonidine

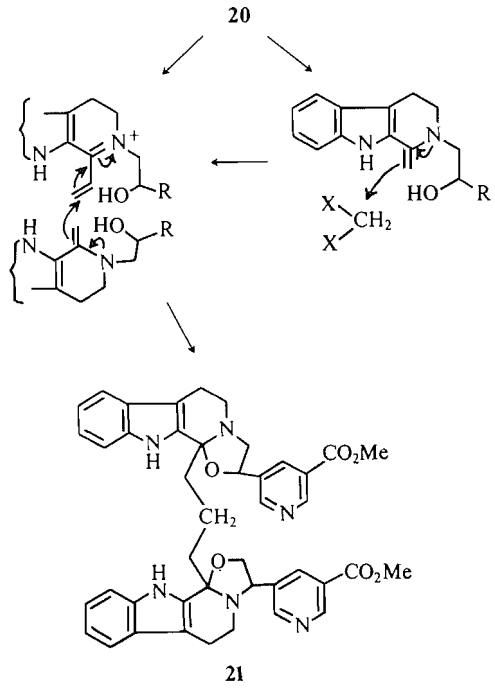
natural and synthetic materials corresponded in every important respect, and the differences that were observed could be confidently attributed to the presence of small amounts of impurities in the natural material, which had been difficult to isolate and purify (1*b*). Furthermore, the synthetic material was available in larger quantities than the natural material and its solution spectra showed better resolution.

The precursor required for the synthesis of ND-305B was the epoxide of 3-vinylpyridine, and this was conveniently prepared by treatment of 3-pyridinecarboxaldehyde with dimethyloxosulfonium methylide (7). The oily product darkened rapidly (reference has been made above to the report (5) of the instability of its 4-isomer), and freshly prepared epoxide was used without further purification in the reaction with harmalan. Synthetic ND-305B was obtained in 32% yield; the correspondence between natural and synthetic materials exactly parallels that described for ND-363C. Once again, better resolution could be obtained in the nmr spectrum of synthetic material; the high field methyl signals were, for example, clearly resolved into two singlets, both removed by treatment with D_2O.

Each of the substances ND-305B and ND-363C is, therefore, a pair of epimers based on structure **18**. Although the pairs have not been separated, and they may, in fact, be inseparable in practice, it is convenient now to assign the alkaloids the names naucleonine and naucleonidine (ND-305B and ND-363C, respectively) with the arbitrary designation of relative configuration shown in **19** and **20**.

Attention may now be drawn to a constituent which received the laboratory designation ND-363B since its mass spectrum indicated that it had the same molecular weight as ND-363C; in fact, the two mass spectra appeared to be very similar indeed (8). Most of the other spectroscopic data were also very similar and it was initially thought that ND-363B was an impure sample of ND-363C and it was not, therefore, included in our earlier listing of isolated constituents (1). The nmr spectrum of ND-363B, while not well resolved, resembled that of ND-363C but had the appearance of an out-of-focus picture or one seen with double vision; the 'doubled' spectrum of ND-363C seemed to have 'doubled' again, particularly in some regions. However, the most obvious difference was that ND-363B lacked the τ 8.22 peak of ND-363C, but since there was, at first, no satisfactory

explanation for the presence of this peak in the spectrum of ND-363C and it was thought to be caused by some degree of hydration of the molecule, its absence in ND-363B seemed to be associated with the mode of preparation of the sample. It is now clear that this explanation can not be correct since the established structure for naucleonidine, **20**, must be modified more significantly to accommodate the observations. One apparent possibility was that ND-363B was a dimer of the assigned formula that fragmented readily to **20** in the mass spectrometer. The availability of field desorption mass spectrometry offered a means of testing this hypothesis, and when the mass spectrum was obtained by this technique. ions of approximately double the originally assigned mass were indeed found at low operating temperatures, but these disappeared at higher temperatures. With the technique used there is more uncertainty than with electron impact mass spectrometry in determining exact molecular weights; besides the problems associated with calibration of the *m/e* range there is uncertainty concerning the probability of ion–molecule reactions. Nevertheless, the values, *m/e* 741 and 739, assigned to the ions observed in the high mass range are too high to be associated with a simple dimer, but could arise from a homolog of the dimer. Furthermore, there are two ions, *m/e* 364 and 376, in the intermediate mass range that could be associated with a monomeric fragment and its homolog. A reasonable explanation for these observations is that ND-363B has a structure such as **21** in which two molecules of naucleonidine (enamine tautomer) have condensed, *in vitro* or *in vivo*, with a one-carbon unit equivalent to formaldehyde. The mass spectrum would then result from a ready fragmentation effectively reversing the last synthetic step, the complexity of the nmr spectrum would be associated with the diastereoisomeric possibilities implied by **21**, and this would not show the τ 8.22 methyl signals of naucleonidine. The signals for the methylene protons that replace the methyl groups of naucleonidine can not be recognized with confidence in the higher field envelope, but treatment of the sample with D_2O causes a marked reduction in the integrated area of the signals near τ 7.9, as would be expected by analogy with the behavior of naucleonidine. It is clear that



alternative modes of condensation can be suggested and that structure **21** is used to provide a concrete illustration of a plausible type of condensation product.

Among the substances of the fourth group was an amorphous material which was believed to be a glycosidic alkaloid, but it appeared to be too involatile to give a satisfactory mass spectrum and its constitution was not determined (1*c*). This alkaloid has now been assigned structure **22** (2*a*). Acetylation provided an amorphous product which was purified chromatographically and analyzed. While the results were of limited value at this stage, they were compatible with a hypothesis that the product was a pentaacetate with a molecular weight of about 790; when the structure was eventually assigned to the alkaloid, these results were in accord with the calculated values for the pentaacetate of **22**, provided the sample retained a molecule of solvent. Subsequently, when field desorption mass spectrometry became available, the results obtained with the alkaloid itself and its pentaacetate were in accord with the formula $C_{27}H_{34}N_2O_{10}$ assigned to the alkaloid.

The most decisive structural evidence was obtained from the 220 MHz nmr spectra of the

alkaloid and its pentaacetate. By associating the integrated areas of certain key signals with an appropriate number of protons in a rational way, it was possible to recognize that the spectra indicated that the substance was a monoglycoside of an indolic alkaloid of the expected molecular weight. The features associated with the indolic portion of the molecule, the methyl β-alkoxyacrylate, and the glycosidic part (acetylated in the case of the derivative) could be recognized; correlations are available which give evidence that the latter feature is a β-glucoside (9). A detailed listing of these spectra has already been given (2*a*) and will not be repeated here, but attention can be drawn to the remaining features in the spectra, mainly associated with rings D and E of structure **22**, the portion of the molecule that is presumably of terpenoid origin. The protons associated with the contiguous positions 3, 14, and 15 in the alkaloid could be recognized and specific decoupling experiments showed coupling constants of 10 Hz between H-3 (τ 6.14) and H-14b (τ 8.26) and 9.5 Hz between H-14b and H-15 (τ 6.97) which established the structure and stereochemistry assigned to this portion of the molecule; similar critical values were found for the pentaacetate, but some of the minor details could not be seen as clearly in this spectrum. The features associated with the chain comprised of positions 18, 19, 20, and 21 were, however, more clearly visible in the spectrum of the pentaacetate than in that of the free alkaloid: H-18a (τ 7.04) was coupled, J = 5 Hz, to H-19 (τ 4.60), which was also coupled, J = 6 Hz, to H-18b (τ 6.77) and, J = 1.5 Hz, to H-20 (τ 7.24), which was coupled further, J = 5 Hz, to H-21 (τ 4.50; doublet). Each of these couplings was established by a decoupling experiment, but the coupling between H-15 and H-20 could not be established in this manner because the chemical shifts are not sufficiently different in the alkaloid or its pentaacetate; in the alkaloid, a simple analysis of the spectrum showed that H-15 and H-20 each had an unassigned coupling, J = 6 Hz, and this was, by elimination, considered to be their mutual coupling. The structural and stereochemical features of rings D and E were assigned from these data. It can be noted that, since ring D is seven-membered, the stereochemical features based on coupling constants are not as secure as they would have been for a six-membered ring; furthermore, some of the values which could be measured for both the alkaloid and its acetylated derivative showed differences, presumably associated with conformational effects caused by having either OH or OAc at C-19. The values of $J_{19,20}$ (3.5 Hz) and $J_{20,21}$ (8.5 Hz) were both larger in the unacetylated alkaloid. Nevertheless, we feel that the weight of the evidence favors the assigned structure **22** for the alkaloid.

Brown and Fraser (10) have isolated an alkaloid from *Anthocephalus cadamba* to which they assign structure **22**; they assign structure **23** to a congener, cadambine, which can be interrelated with **22** by chemical transformations. Cadambine contains the interesting oxazolidine feature we have found in naucleonine, **19**, and naucleonidine, **20**, and its oxygen atom bridging the seven-membered ring of cadambine can be expected to lead to greater conformational rigidity. The type of evidence that Brown and Fraser adduce is similar to ours but, since they had both **22** and **23** available, they have taken their stereochemical conclusions further than we have. Nevertheless, the conclusions regarding **22**, which should now be called 3α-dihydrocadambine, were reached independently, and since the identity of samples of the pentaacetate prepared in the two laboratories has been established on the basis of spectroscopic and chromatographic criteria, the evidence and conclusions of both groups are corroborative, and the assignments made are additionally secure.

It may be noted in passing that structure **24** was suggested previously for the indole-pyridine alkaloid nauclechine (1*b*) on independent evidence. Although no further evidence from direct studies of nauclechine is available yet, the assignment of structure **22** to dihydrocadambine makes the assignment of **24** to nauclechine increasingly attractive.

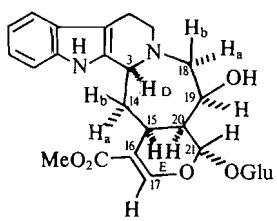
Attention may now be drawn to another alkaloid that was placed in the fourth category and designated ND-370 (1*c*). A considerable amount of spectroscopic data was obtained for this crystalline alkaloid, mp 209–211 °C, which was obtained in very small amounts: the formula $C_{21}H_{26}N_2O_4$ was assigned to it from mass spectrometry, it was clearly an indole alkaloid and its formula suggested that it was derived from a tryptamine unit and a C_9-terpenoid unit.

TABLE 1. Nuclear magnetic resonance spectrum and assignments to ND-370, **25**

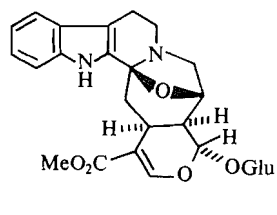
Proton§	Chemical shift (τ)	Multiplicity	Coupling constants (Hz)
1†	1.62	broad s	—
5a,b 6a,b	6.8–7.4	m	—
9, 10, 11, 12	2.4–3.0	m	—
14a,b† 15	8.2–8.4	m	—
16a	8.60	dd	$J_{16a,16b} = 12$; $J_{16a,17} = 10$*
16b	8.14	ddd	$J_{16b,16a} = 12$; $J_{16b,17} = 2.5$*; $J_{16b,15} = 3$
17	5.18	dd	$J_{17,16a} = 10$*; $J_{17,16b} = 2.5$*
18a	6.07	d	$J_{18a,18b} = 10.5$*
18b	7.28	m	$J_{18b,18a} = 10.5$*; $J_{18b,19} = 6.5$*
19	5.46	dd	$J_{19,18a} = 6.5$*; $J_{19,20} = 2$*
20	7.93	ddd	$J_{20,15} = 12$; $J_{20,19} = 2$*; $J_{20,21} = 3.5$*
21	5.08	d	$J_{21,20} = 3.5$*
OMe	6.46	s	—
OMe	6.55	s	—

*Coupling constants demonstrated by explicit decoupling experiment (the others are deduced from splitting patterns).
§Integrated areas are in accord with the numbers of protons assigned.
†The addition of D_2O/MeOD removes the signals associated with these protons.

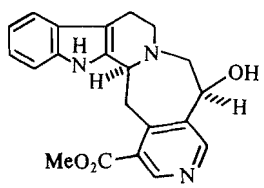
The nmr spectrum, which supplied some of the evidence for the above conclusions, clearly showed the presence of two methoxyl groups in the molecule, but it appeared to be too complex to interpret further in structural terms. The uv spectrum was of interest since it strongly resembled those of naucleonine and naucleonidine, particularly with respect to its p*H* dependence. Since the structures of naucleonidine and naucleonine were not established at that time, this information was of limited assistance; however, now that the structures of these alkaloids have been established and the uv characteristics have been associated with the oxazolidine unit, a feature also observed in the case of cadambine (10), it is logical to expect that ND-370 contains this structural unit, and we have reassessed the data obtained previously in the light of this proposal and experience gained with this class of alkaloids. Structure **25** accommodates all of the data presently available and represents a rational hypothesis for the structure of ND-370.



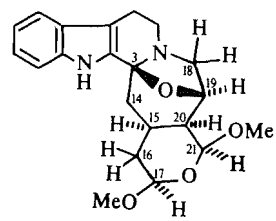
22



23



24



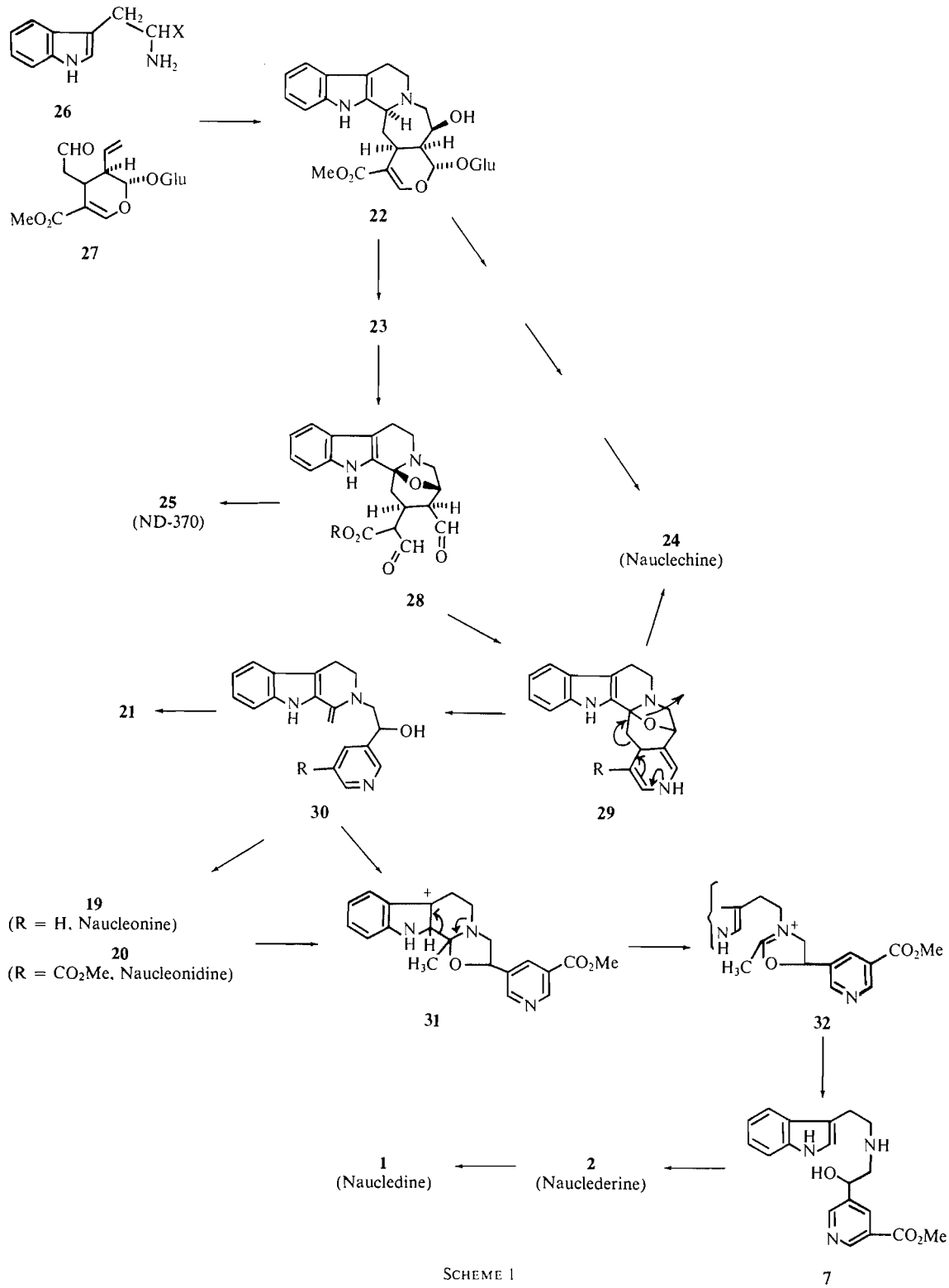
25

The mass spectrum of ND-370 had been studied in considerable detail (8); the formulae of important fragment ions had been assigned from accurate mass measurements, and a number of metastable ion transitions had been established (1*c*). All of these data are compatible with the fragmentation pattern expected for an ion produced from a molecule of formula **25**. The 100 MHz nmr spectrum had also been examined in considerable detail (8), and it is now shown in convenient form in Table 1. The interpretation

of this spectrum in the light of more recent experience is the principal basis on which we have made the assignments shown, leading to the structural proposal **25**; the 220 MHz spectrum was also examined subsequently, but in this case it provided no further structural information, although it did help to reinforce some of the assignments. The assignments to the tryptamine-derived portion of the molecule (H-1–H-12) and the methoxyl groups are straightforward. A key assignment for the rest of the molecule is that of H-19: its chemical shift is appropriate for its environment and it has been shown by decoupling experiments to be coupled to a proton, H-18b, which is part of a methylene group, and to H-20 which is also coupled (demonstrated by decoupling) to H-21 (τ 5.08; at a carbon bearing two oxygen substituents) as well as to another proton (presumed to be H-15). The other proton, H-17, assigned to a carbon bearing two oxygen substituents, is coupled to the protons of a methylene group, H-16a,b, which are coupled to a single proton, H-15. Unfortunately, it has not been possible to disentangle the signals assigned to H-15 and the adjacent methylene group, H-14a,b. The continuous chain encompassing C-18 to C-21 seems well established, and the coupling constants are in accord with a *cis* relationship of the hydrogens at C-19, C-20, and C-21. The data for the C-14 to C-17 chain are less explicit, but, wherever specific assignments can be made, are in accord with the proposed structure. The apparent coupling between H-20 and H-15 is 12 Hz, considerably larger than in cadambine and dihydrocadambine (2*a*, 10), and this leads to difficulties in making stereochemical assignments to the remaining centres that are consistent with the coupling constant data, particularly if the *cis* relationship assigned to the ring fusion in cadambine and dihydrocadambine is assumed to be retained. Although the quality of the data does not allow the structural assignment to be made as securely as was the case with 3α-dihydrocadambine, the proposed structure **25** is an attractive working hypothesis, and the observation that the hydrogens of the methylene group assigned to C-14 can be exchanged with D_2O is what is expected on the basis of precedent, and provides support for the present assignments.

It can now be seen that the alkaloidal constituents of *N. diderrichii* form a substantial array of structural types, many of which seem, at first glance, to bear little chemical resemblance to one another. Nevertheless, closer examination shows that a pattern unfolds which allows the various members to be interconnected by rational and reasonable chemical reactions. These transformations may represent actual steps in the formation of the alkaloids either in a biosynthetic sense or as accidental reactions forming artifacts during the isolation process (1*c*). Although it is possible only to speculate about the reactions, the pattern becomes apparent on examination of Scheme 1.

There is ample evidence to expect that these alkaloids are derived from tryptophan or tryptamine, **26**, and a terpenoid component which in the final pre-alkaloidal stage is represented by secologanin, **27** (11). It is clear that dihydrocadambine, **22**, contains these units structurally intact with only a minimal chemical modification, an oxidation. This oxidation involves transforming the vinyl group to an epoxide equivalent, probably after the initial condensation forming vincoside (11), and reaction of this unit with the amino function can lead to the hydroxylated seven-membered ring. (It seems likely that the alkaloids of *N. latifolia* (12) arise by a sequence corresponding to that outlined below, but without formation of this seven-membered ring; instead, lactamization occurs at a subsequent stage.) A further oxidation would form cadambine, **23**, and obvious modifications would lead to isodihydrocadambine (10) and rubenine, 13, which have been isolated from related species. Hydrolysis of **23** leads to a key intermediate, which can be represented in a formal manner as the carboxydialdehyde **28**: decarboxylation and cyclization in the presence of methanol leads to the ketal **25** (ND-370); reaction of **28** with ammonia or its equivalent, either with or without a decarboxylation step, leads to the dihydropyridines **29** which, by the fragmentation shown can form the pyridines **30** that have been shown to be tautomers of naucleonine and naucleonidine (**19**, **20**); reference has already been made to the formation of **21** from **30** (R = CO_2Me). An alternative opening and rearrangement of **29** (R = CO_2Me) leads to its isomer nauclechine, **24**; alternatively, **24** could be formed from **22** by conversion to the corresponding dihydropyridine, followed by oxidation to the pyridine. The formation of naucledérine, **2**, requires the loss of a two-carbon unit and it is rational to look for this from



SCHEME 1

naucleonidine (or a tautomer) where fragmentation has already opened up such a unit; a suggestion of how this could occur through **31** and **32**, leading to the synthetic precursor **7** of **2**, is offered. Naucledine, **1**, chemically the simplest of the indole-pyridine alkaloids, is almost certainly the one that has suffered the greatest chemical change; it is the only one in which the two-carbon unit at a 3-pyridyl position has been eroded to a single carbon, and it seems probable that it represents an oxidative ring contraction product of naucledérine, **2**. Although other routes to them can certainly be proposed, it is interesting to speculate that some, at least, of the simple β-carboline and pyridine alkaloids isolated from this plant (*1a*) may also have been formed by fragmentation of more complex molecules appearing in Scheme 1.

Experimental

Melting points were determined on a Thomas–Kofler micro hot stage. Spectrometers used were a Perkin-Elmer 237B for ir spectra, a Unicam SP 800A for uv spectra, a Varian HA-100 for routine nmr spectra (100 MHz), a Varian HR-220 (at the Canadian 220 MHz NMR Centre) for 220 MHz nmr spectra, a CEC 21-490 for routine mass spectra, an AEI MS-902 for accurate mass measurements, and a Varian CH5 (at the University of Windsor) for field desorption mass spectra. Unless otherwise indicated, chloroform solutions were used to obtain ir spectra and the wavelengths of significant absorptions are reported in μm, methanol solutions were used to obtain uv spectra (MeOH–HCl or MeOH–KOH means that one drop of 5% hydrochloric acid or aqueous potassium hydroxide was added to the sample cell) and the wavelengths of absorption maxima (λ_{max}) are reported in nm followed by the extinction coefficient (ε) in parentheses, and chloroform-*d* solutions (with tetramethylsilane as internal standard) were used to obtain nmr spectra and chemical shifts are reported on the τ scale followed in parentheses with an indication of the multiplicity of the signal (initial letter abbreviations for singlet, doublet, etc.; the letter is placed in quotation marks when the multiplicity is only apparent) and the number of protons associated with it. Routine mass spectra were determined at 70 eV and the *m/e* values of significant ions are reported followed in parentheses by the height of the peak relative to the base peak (100%). Merck precoated silica gel F254 plates (0.5 mm analytical, 2.0 mm preparative) with a fluorescent indicator were used for tlc unless otherwise indicated; the common elution system 85:14:1 methylene chloride – methanol – concentrated ammonia is abbreviated as m-m-a.

1-(5′-Carbomethoxy-3′-picolyl)tetrahydro-β-carboline **3**

3-Diazoacetyl-5-carbomethoxypyridine, **6** (*X* = CHN_2)

A solution of the acid chloride **6** (X = Cl) (*1a*) (2 g, 10 mmol) in 150 ml of ether was added dropwise with stirring over a period of 15 min to a cold ethereal solution of diazomethane (20 mmol), prepared from bis(*N*-methyl-*N*-nitroso)terephthalimide and distilled. The reaction mixture was stirred under nitrogen for a further 2 h, filtered, and the diazo ketone **6** (X = CHN_2) was obtained in quantitative yield by evaporation of the solvent. An analytical sample (decomposed before melting) was recrystallized from chloroform–ether. *Anal.* calcd. for $C_9H_7N_3O_3$: C 52.68, H 3.44, N 20.48; found: C 52.67, H 3.47, N 20.37. Spectroscopic characteristics: ir 4.72, 5.79, 6.16, 7.37; nmr 0.73 (d, *J* = 2 Hz, 1H), 0.89 (d, *J* = 2 Hz, 1H), 1.44 ('t', 2 Hz spacing, 1H), 3.88 (s, 1H), 5.99 (s, 3H); ms 205 (100), 177 (30), 174 (16), 164 (57), 149 (14), 146 (46), 136 (28), 118 (33), 106 (15), 90 (17), 78 (10), 63 (13).

1-(5′-Carbomethoxy-3′-picolyl)dihydro-β-carboline, **4**

The diazo ketone **6** (X = CHN_2) (3.90 g, 19.0 mmol) was added to a stirred solution of tryptamine (3.62 g, 22.6 mmol) in 160 ml of dry dioxane at 55 °C under nitrogen, and freshly prepared silver oxide (1.4 g) was then added in portions over an 18 h period. Stirring was continued for a further 6 h, and during the reaction period the bath temperature was allowed to rise to 100 °C. Filtration and evaporation afforded a brown foam which was dissolved in methanol and passed through a short alumina column. Slow addition of ether caused the tryptamide **5** to separate as an oil (1.83 g, 28% yield) which was collected. Spectroscopic characteristics: ir (CH_3CN) 5.80, 6.00; nmr (DMSO-d_6/$CDCl_3$) −0.55 (br, 1H), 1.00 (d, *J* = 2 Hz, 1H), 1.33 (d, *J* = 2 Hz, 1H), 1.78 ('t', 2 Hz spacings, 1H), 1.90 (t, *J* = 6 Hz, 1H), 2.33–3.10 (complex, 5H), 6.10 (s, 3H), 6.33–6.82 (complex, 4H), 7.12 ('t', 7 Hz spacings, 2H); ms 337 (13), 316 (14), 144 (14), 143 (100), 130 (57); high resolution ms 337.1426 ($C_{19}H_{19}N_3O_3$: 337.1426).

The tryptamide **5** (250 mg, 0.74 mmol) was suspended in 17 ml of freshly distilled phosphorus oxychloride and refluxed for 2 h under nitrogen. Evaporation under reduced pressure afforded a brown residue which was dissolved in dilute acetic acid, filtered, and the filtrate was made basic with dilute aqueous ammonia. A brown solid (200 mg) was obtained by chloroform extraction and evaporation of the chloroform. A concentrated chloroform solution of this solid slowly deposited the dihydro-β-carboline **4** (93 mg, 38% yield) as a yellow solid. An analytical sample, mp 194–203 °C (dec.), was recrystallized from methanol. *Anal.* calcd. for $C_{19}H_{17}N_3O_2$: C 71.45, H 5.37, N 13.16; found: C 71.09, H 5.21, N 12.92. Spectroscopic characteristics: ir (KBr) 5.81; uv 213 (21 700, end absorption), 245 (sh), 324 (10 900), 352 (sh); nmr (8:2 DMSO-d_6/$CDCl_3$) −0.55 (br, 1H), 1.15 (d, *J* = 2 Hz, 1H), 1.24 (d, *J* = 2 Hz, 1H), 1.76 ('t', 2 Hz spacings, 1H), 2.34–3.04 (complex, 4H), 3.91 (m, 0.75H), 4.15 (s, 0.75H), 5.82 (s, 0.5H) (the preceding three signals together correspond to 2 protons, addition of D_2O removes all three signals), 6.02 (s, 3H); 6.53 (br, 2H, after addition of D_2O, signal is 't', 6 Hz spacings, 2H), 7.10 ('t', 6 Hz spacings, 2H); ms 319 (3), 318 (4), 317 (3), 316 (3), 168 (8), 145 (12), 138 (12), 131 (5), 130 (9), 106 (31), 105 (28), 87 (7), 85 (63), 83 (100), 77 (20).

A solution of sodium borohydride (29 mg, 0.76 mmol) in 2 ml of methanol was added to a stirred suspension of

the dihydro-β-carboline (122 mg, 0.38 mmol) in 14 ml of methanol at 5 °C under nitrogen, and 5 ml of diglyme was added to effect solution. After the solution had been stirred at 5 °C for 5.5 h, the tetrahydro-β-carboline **3** was isolated in the usual manner in quantitative yield as a beige solid. Spectroscopic characteristics: ir 290 (sharp), 3.03 (br), 5.80; uv 226 (24 800, end absorption), 275 (6950), 291 (sh); nmr (1:9 DMSO-d_6/$CDCl_3$) −0.14 (br, 1H), 0.97 (d, J = 2 Hz, 1H), 1.33 (d, J = 2 Hz, 1H), 1.76 ('t', 2 Hz spacings, 1H), 2.40–3.07 (complex, 4H), 5.73 (m, 1H), 6.08 (s, 3H), 6.60–7.50 (complex, 6H), 7.76 (br, 1H); ms 321 (3), 320 (15), 319 (64), 318 (59), 317 (57), 316 (17), 304 (11), 258 (10), 172 (15), 171 (100), 129 (13), 115 (14), 85 (10), 83 (17); high resolution ms 321.1466 ($C_{19}H_{19}N_3O_2$: 321.1477).

The Model Phenylhexahydroazepinoindole, ***10***

N,N-Bis(2-phenyl-2-hydroxyethyl)tryptamine, ***9***

Styrene oxide (5.24 g, 43.7 mmol), prepared by treatment of styrene bromohydrin with sodium hydride, was added to molten tryptamine (3.50 g, 21.9 mmol) and stirred at 135 °C for 3 h. Unchanged styrene oxide was removed at 135 °C/0.1 torr. When the melt was allowed to cool, the disubstituted product **9** formed a glassy unstable solid. Spectroscopic characteristics: ir 2.77 (sharp), 2.87 (sharp), 2.84–3.05; nmr 1.73 (br, 1H), 2.40–3.12 (complex, 15H), 5.39 (m, 2H), 6.43 (br, 2H, removed by D_2O), 7.45–6.87 (complex, 8H); ms 364 (8), 232 (13), 144 (16), 143 (26), 132 (15), 131 (13), 130 (42), 129 (22), 120 (14), 118 (13), 117 (11), 107 (16), 106 (70), 105 (98), 104 (35), 103 (28), 102 (11), 91 (46), 90 (15), 89 (12), 78 (24), 77 (100), 76 (14), 69 (14), 64 (15), 57 (27), 56 (14), 55 (28), 52 (14), 51 (48), 50 (27).

N-(2-Phenyl-2-hydroxyethyl)tryptamine, ***8***

The monosubstituted product was prepared as a mixture with the disubstituted product (**8**:**9** of 45:55) by the addition of styrene bromohydrin to an equivalent amount of tryptamine in a boiling solution of sodium bicarbonate in aqueous methanol. The mixture could be separated by tlc with methanol elution. A more convenient preparation is the following. α-Acetoxyphenylacetyltryptamine was prepared from tryptamine and *O*-acetylmandelyl chloride (14) in the usual way. It was obtained in 75% yield as an uncrystallizable semisolid. This material (2.8 g) was refluxed for 6 h in 70 ml of 3% methanolic hydrogen chloride and α-hydroxyphenylacetyltryptamine was obtained in 96% yield. An analytical sample, mp 183.5–185 °C, was obtained by recrystallization from methanol. *Anal.* calcd. for $C_{18}H_{18}N_2O_2$: C 73.45, H 6.16, N 9.52; found: C 73.39, H 6.21, N 9.48. Spectroscopic characteristics: ir (Nujol) 2.97 (sharp), 3.03 (sharp), 3.11 (br), 6.11, 6.49; nmr (DMSO-d_6) −0.83 (br, 1H), 1.95 (m, 1H), 2.23–3.06 (complex, 10H), 3.82 (d, J = 5 Hz, 1H), 5.02 (d, J = 5 Hz, 1H), 6.55 (4 peaks, 7 Hz spacings, 2H), 7.13 (3 peaks, 7 Hz spacings, 2H); ms 294 (2), 276 (18), 220 (11), 144 (20), 143 (100), 132 (11) 130 (49), 77 (15).

The α-hydroxyphenylacetyltryptamine (1.30 g, 4.4 mmol) in 10 ml of dry tetrahydrofuran was added dropwise to a stirred suspension of lithium aluminum hydride (0.59 g, 15.5 mmol) in 40 ml of dry tetrahydrofuran and refluxed under nitrogen for 20 h. Work up by treatment with aqueous sodium hydroxide followed by an acid–base separation provided the hydroxy amine in 55% yield, and an analytical sample, mp 116–117 °C, was obtained by recrystallization from methanol. *Anal.* calcd. for $C_{18}H_{20}N_2O$: C 77.11, H 7.19, N 9.99; found: C 76.83, H 7.03, N 9.89. Spectroscopic characteristics: ir 2.88 (sharp), 3.02 (br); nmr 1.72 (br, 1H), 2.30–3.00 (complex, 9H), 5.32 (dd, J = 8 and 4 Hz, 1H), 6.40 (br, 2H, removed by D_2O), 7.05 (complex, 6H); ms 262 (9), 171 (8), 160 (7), 132 (7), 131 (18), 130 (37), 123 (11), 122 (91), 106 (24), 105 (100), 78 (9), 77 (64), 51 (17), 44 (23), 40 (44).

Diacetyl derivative: ir 5.76, 6.12; nmr 1.6 (br, 1H), 2.4–3.2 (complex, 10H), 3.95 (complex, 1H), 6.2–6.8 (complex, 4H), 7.06 (complex, 2H), 7.97 (s, 4H), 8.11 (s, 2H). (The complexities of the spectrum are attributed to the presence of two rotamers.)

The disubstituted tryptamine **9** (136 mg, 0.36 mmol) was stirred in 4.8 g of polyphosphoric acid at 88 °C under nitrogen for 6.5 h, and then water was added to the hot reaction mixture. After it had cooled, the reaction mixture was made basic with aqueous ammonia, and extracted with methylene chloride. The extract afforded a brown oil which was purified by preparative tlc with m-m-a elution. The product (28 mg, 22% yield) was identical in ir, nmr, and tlc characteristics with a sample of **10** provided by K. Freter (4).

These reaction conditions converted the monosubstituted tryptamine **8**, to **10** in 26% yield.

Naucledérine, ***2***

Chilled 48% hydrobromic acid was slowly added dropwise to freshly prepared 3-diazoacetyl-5-carbomethoxypyridine (**6**, X = CHN_2) with stirring and cooling until a slight excess of the acid was present. The paste obtained was suction filtered and washed with cold acetone, leaving the hydrobromide of the bromo ketone **6** (X = Br) as beige crystals (7.74 g, 77% yield). An analytical sample (darkens but does not melt below 355 °C) was recrystallized from methanol–ether. *Anal.* calcd. for $C_9H_9NO_3Br_2$: C 31.91, H 2.68, N 4.13, Br 47.10; found: C 31.94, H 2.70, N 4.28, Br 46.88. Spectroscopic characteristics: ir (KBr) 3.9 (br), 5.75, 5.77, 5.85; nmr (methanol-d_4) 0.63 (br, 1H), 0.86 (br, 2H), 5.92 (s, 3H), 6.15 (s, 2H).

Sodium borohydride (475 mg, 12.5 mmol) in 20 ml of methanol was added dropwise to a stirred solution of the bromo ketone hydrobromide (4.25 g, 12.5 mmol) in 220 ml of methanol cooled to 1 °C. Stirring was continued at 1 °C for 7 min and then at 25 °C for 25 min. A second portion of sodium borohydride (475 mg, 12.5 mmol) in 20 ml of methanol was then added. Methanol was removed under reduced pressure, water containing a few drops of acetic acid was added to the residue, and the mixture was extracted with methylene chloride. The extract afforded a product which proved to be a mixture of the bromohydrin (68% yield) and the epoxide **11** (85:15). A sample of the bromohydrin was purified by preparative tlc with elution by 95:5 chloroform–methanol and obtained as an amorphous solid. Spectroscopic characteristics: ir 2.80 (sharp), 3.10 (br), 5.80; nmr 0.90 (d, J = 2 Hz, 1H), 1.22 (d, J = 2 Hz, 1H), 1.62 ('t', 2 Hz spacings, 1H), 4.92 ('t', 6 Hz spacings, 1H), 5.25 (br, 1H),

6.03 (s, 3H), 6.38 (d, J = 6 Hz, 2H); ms 261 (1), 259 (1), 243 (1), 241 (1), 230 (3), 228 (3), 166 (100), 134 (13), 78 (10), 74 (14), 59 (27), 45 (14), 44 (14); high resolution ms 258.9845, 260.9825 (equal intensity) ($C_9H_{10}NO_3Br$: 258.9845, 260.9825).

The mixture of products was not normally separated, but carried forward to the next step, in which it was stirred with a twofold excess of sodium hydride in dry tetrahydrofuran at 25 °C for about 24 h. The reaction mixture was filtered, concentrated to an oil, and partitioned between water and methylene chloride. The organic layer afforded the epoxide **11** (93% yield) as an amorphous solid. Sublimation at 60 °C/0.05 torr provided an analytical sample, mp 63.5–64.5 °C. *Anal.* calcd. for $C_9H_9NO_3$: C 60.33, H 5.06, N 7.86; found: C 60.11, H 5.25, N 7.89. Spectroscopic characteristics: ir 5.80; nmr 0.87 (d, J = 2 Hz, 1H), 1.28 (d, J = 2 Hz, 1H), 1.85 ('t', 2 Hz spacings, 1H), 6.03 (superimposed s and m, 4H), 6.82 (m, J = 5.8 and 4.1 Hz, 1H), 7.18 (m, J = 5.8 and 2.5 Hz, 1H); ms 179 (63), 178 (54), 164 (11), 151 (44), 150 (30), 148 (45), 134 (11), 121 (10), 120 (100), 119 (13), 106 (38), 92 (23), 78 (22), 65 (27), 63 (27), 59 (16).

A solution of the epoxide **11** (550 mg, 3.1 mmol) in 4 ml of methanol was added over a 2 h period to a solution of tryptamine (1.08 g, 6.8 mmol) in 4 ml of refluxing methanol under nitrogen, and reflux was continued for a further 1.5 h. The methanol was removed under reduced pressure and the residue containing mono- and disubstituted products was purified by preparative tlc with m-m-a elution. The major fraction isolated in 46% yield was the amino alcohol **7** which was obtained as an amorphous solid. Spectroscopic characteristics: ir 2.88 (sharp), 3.0 (br), 5.80; nmr 0.94 (d, J = 2 Hz, 1H), 1.10 (br, 1H), 1.32 (d, J = 2 Hz, 1H), 1.72 ('t', 2 Hz spacings, 1H), 2.26–3.17 (complex, 5H), 5.26 (m, 1H, after D_2O treatment, dd, J = 8 and 4 Hz, 1H), 6.02 (s, 3H), 6.60 (br, 2H), 6.9–7.2 (complex, 6H); ms 339 (4), 321 (10), 223 (38), 209 (22), 193 (14), 192 (11), 191 (59), 187 (40), 174 (17), 173 (44), 168 (11), 167 (40), 166 (10), 165 (27), 164 (16), 144 (95), 143 (36), 134 (27), 132 (18), 131 (100), 130 (90), 129 (24), 117 (15), 106 (16), 78 (12), 77 (12), 58(16), 57(14); high resolution ms 339.1583 ($C_{19}H_{21}N_3O_3$: 339:1583).

Diacetyl derivative: ir 2.88 (sharp), 5.81 (br), 6.12; nmr 0.66 (br, 1H), 0.81 (d, J = 2 Hz, 1H), 1.22 (d, J = 2 Hz, 1H), 1.70 ('t', 2 Hz spacings, 1H), 2.12–3.06 (complex, 5H), 3.80 (dd, J = 8 and 4 Hz, 1H), 6.02 (s, 3H), 6.13–6.60 (complex, 4H), 6.72–7.22 (complex, 2H), 7.87 (s, 4H), 8.03 (s, 2H). (The complexities of the spectrum are attributed to the presence of two rotamers.)

The disubstituted tryptamine was isolated as a mixture of diastereoisomers in 8% yield. Spectroscopic characteristics: ir 2.88 (sharp), 2.94 (br), 5.80; nmr 0.90 (br, 2H), 1.16 (br, 1H, removed by D_2O), 1.30 (d, J = 2 Hz, 1H), 1.40 (d, J = 2 Hz, 1H), 1.70 (br, 2H), 2.20–3.14 (complex, 5H), 5.26 (complex, 2H), 5.70 (br, 2H), 6.01 (s, 6H), 6.72–7.43 (complex, 8H).

The hydroxy amine **7** (823 mg, 2.5 mmol) was mixed with 40 g of polyphosphoric acid under nitrogen and stirred at 95 °C for 8 h. The reaction mixture was cooled, made basic with chilled dilute ammonia, and extracted with methylene chloride. The extract afforded a product which was purified by preparative tlc with m-m-a elution. Naucledérine, **2**, (42 mg, 5.4% yield) was obtained as an oil that was recrystallized from methanol to give crystals, mp 94–108 °C. *Anal.* calcd. for $C_{19}H_{19}N_3O_2$: C 71.01, H 5.96, N 13.08; for $C_{19}H_{19}N_3O_2 \cdot H_2O$: C 67.24, H 6.24, N 12.38, for $C_{19}H_{19}N_3O_2 \cdot CH_3OH$: C 67.97, H 6.56, N 11.89; found: C 67.13, H 6.13; by ultramicro analysis: C 67.19, H 6.70, N 11.61. High resolution ms 321.1474 ($C_{19}H_{19}N_3O_2$: 321.1477), 292.1212 ($C_{18}H_{16}N_2O_2$: 292.1212), 279.1132 ($C_{17}H_{15}N_2O_2$: 279.1133).

The ir, uv, nmr, and ms characteristics of the synthetic material and natural naucledérine (1*b*) were identical in all significant aspects; their tlc behavior was identical on silica gel (3 systems) and on alumina.

The Dihydro-β-carbolines, ***13***

1-(3'-Hydroxypropyl)dihydro-β-carboline, ***13*** *(R = H)*

A solution of tryptamine (1.60 g, 10.0 mmol) and γ-butyrolactone, **15** (R = H) (0.92 g, 10.7 mmol) in 2 ml of absolute ethanol was refluxed under nitrogen for 27 h. The solvent was removed on a rotary evaporator and the gummy residue was triturated with carbon tetrachloride, leaving the tryptamide **14** (R = H) as a crystalline solid (2.34 g, 9.5 mmol), mp 67–73 °C. Spectroscopic characteristics: ir 2.89, 3.0, 6.06; uv 229 (9900), 275 (4850), 282 (5250), 291 (4500); ms 246 (4), 228 (4), 160 (11), 143 (55), 131 (45), 130 (100). This was acetylated with acetic anhydride in pyridine at room temperature for 24 h, and converted to the acetate, mp 92–97 °C, in 89% yield. *Anal.* calcd. for $C_{16}H_{20}N_2O_3$: C 66.64, H 6.99, N 9.72; found: C 66.80, H 6.90, N 9.64. Spectroscopic characteristics: ir 2.88, 3.0, 5.78, 6.01; uv 229 (12 450), 275 (4750), 282 (5250), 291 (4400); nmr 1.14 (br, 1H, removed by $NaOD/D_2O$), 2.37–3.13 (complex, 5H), 4.00 ('t', 6.5 Hz spacings, 1H, removed by $NaOD/D_2O$), 6.00 ('t', 6 Hz spacings, 2H), 6.47 (4 peaks, 6.5 Hz spacings, 2H, after $NaOD/D_2O$ treatment, 't', 6.5 Hz spacings, 2H), 7.03 ('t', 6.5 Hz spacings, 2H), 7.80–8.23 (m, 4H), 8.05 (s, 3H); ms 288 (8), 144 (17), 143 (100), 131 (8), 130 (61).

A mixture of the acetoxytryptamide (563 mg, 1.95 mmol) and 4 ml of freshly distilled phosphorus oxychloride was refluxed under nitrogen for 2 h. Excess phosphorus oxychloride was removed under reduced pressure, and the residue was taken up in 100 ml of 20% aqueous acetic acid. The solution was made basic with solid sodium carbonate and extracted with methylene chloride. The extract afforded a brown oil which was subjected to preparative tlc with m-m-a elution, and the product (192 mg, 36% yield) was obtained as an uncrystallizable gum: ir 2.89, 3.06, 5.80; uv 216 (14 600), 229 (14 350), 235 (14 350), 318 (12 450); in MeOH–HCl 215 (14 350), 247 (10 000), 355 (18 500); nmr 2.23–3.07 (m, 4H), 5.63–6.33 (m, 4H), 6.90–7.43 (m, 4H), 7.57–8.24 (m, 2H), 8.03 (s, 3H); ms 270 (8), 210 (71), 209 (100), 184 (55).

The above product (58 mg, 0.21 mmol) was dissolved in 5 ml of 80% aqueous methanol to which potassium bicarbonate (100 mg, 1.0 mmol) was added, and the solution was refluxed under nitrogen for 10.5 h. The methanol was removed on a rotary evaporator and the residue was partitioned between 50 ml of water and 100 ml of methylene chloride, and the aqueous layer was ex-

tracted with a further 100 ml of methylene chloride. The combined organic layers provided an oil which was purified by preparative tlc with m-m-a elution, and the product **13** (R = H) was obtained as a waxy solid (46 mg, 93% yield). Spectroscopic characteristics: ir 2.88, 3.12; uv 215 (12 500), 236 (11 950), 241 (11 800), 318 (11 900); in MeOH–HCl 214 (12 250), 246 (8300), 353 (19 400); in MeOH–KOH 216 (12 900), 236 (13 000), 314 (13 200); nmr ($CDCl_3/CD_3OD$) 2.23–3.07 (m, 4H), 5.90–6.43 (m, 4H), 6.90–7.40 (m, 2H), 7.80–8.33 (m, 2H); ms 228 (5), 210 (68), 209 (100), 198 (5), 184 (50).

A sample was converted to its hydrochloride salt, mp 186–206 °C (dec.) for analysis. *Anal.* calcd. for $C_{14}H_{17}N_2OCl$: C 63.51, H 6.47, N 10.58; found: C 63.60, H 6.41, N 10.48.

1-(3'-Hydroxy-3'-phenylpropyl)dihydro-β-carboline, ***13*** *(R = Ph)*

A solution of tryptamine (1.60 g, 10.0 mmol) and γ-phenyl-γ-butyrolactone, **15** (R = Ph) (1.74 g, 10.7 mmol) in 2 ml of absolute ethanol was refluxed under nitrogen for 26 h. The solvent was removed on a rotary evaporator and the residue was dissolved in hot methanol and treated with activated charcoal. The clarified solution yielded the tryptamide **14** (R = Ph) as a light yellow gum (3.13 g, 9.6 mmol) that was pure enough for use in the next step. An analytical sample was obtained by tlc with m-m-a elution. *Anal.* calcd. for $C_{20}H_{22}N_2O_2$: N 8.69; found: N 8.44. Spectroscopic characteristics: ir 2.87, 3.0, 6.05; uv 227 (18 150), 275 (5200), 282 (5500), 291 (4700); ms 322 (0.2), 304 (2), 162 (38), 160 (17), 143 (25), 131 (54), 130 (100).

The hydroxytryptamide **14** (R = Ph) was acetylated by stirring it for 18 h with 0.25 ml of acetic anhydride in 1.0 ml of pyridine and 5 ml of methylene chloride under nitrogen. The acetate was obtained in 97% yield as a pale yellow gum: ir 2.87, 3.03, 5.79, 6.03; uv 226 (29 900), 275 (6200), 282 (6600), 291 (5800); nmr 1.0 (br, 1H), 2.2–3.2 (complex, 5H), 4.03 ('t', 6 Hz spacings, 1H), 4.25 ('t', 6 Hz spacings, 1H), 6.47 ('q', 6 Hz spacings, 2H), 7.10 ('t', 6 Hz spacings, 2H), 7.7–8.1 (m, 4H), 8.02 (s, 3H); ms 364 (0.8), 304 (7), 144 (16), 143 (100), 131 (11), 130 (77).

The acetylated material (429 mg) was treated with 5 ml of freshly distilled phosphorus oxychloride in the manner described above. The product was obtained as an uncrystallizable yellow gum (122 mg, 29% yield): ir 2.90, 3.06, 5.78; uv 213 (22 400), 235 (14 200), 318 (11 000); in MeOH–HCl 212 (22 400), 242 (10 250), 356 (15 400); nmr 0.57 (br, 1H), 2.3–3.2 (complex, 9H), 4.20 ('t', 6 Hz spacings, 1H), 6.17 ('t', 8 Hz spacings, 2H), 6.8–8.1 (complex, 6H), 8.03 (s, 3H); ms 346 (2), 288 (9), 287 (29), 286 (100), 285 (73), 284 (13), 210 (6), 209 (32), 184 (49).

The above product (116 mg, 0.34 mmol) was hydrolyzed by refluxing it for 6 h in 5 ml of 80% aqueous methanol containing potassium bicarbonate (100 mg, 1.0 mmol) under nitrogen in the manner described above. The product **13** (R = Ph) was recovered in 83% yield as a yellow oil: uv 216 (18 900), 248 (11 300), 289 (6400), 318 (8500); in MeOH–HCl 214 (18 200), 305 (4700), 352 (12 500); in MeOH–KOH 217 (21 700), 289 (7800), 316 (10 200); nmr ($CDCl_3/CD_3OD$) 2.3–3.1 (complex, 9H), 5.1–5.4 (m, 1H), 6.0–6.5 (m, 2H), 7.0–7.5 (m, 4H), 7.7–8.2 (m, 2H). A sample was converted to its hydrochloride salt, mp 180–220 °C (dec.), for analysis. *Anal.* calcd. for $C_{20}H_{21}N_2OCl$: C 70.47, H 6.21, N 8.22; found: C 70.20, H 6.12, N 8.37.

The Pyridylhydroxypropyl-β-carboline ***13*** *(R = 3-pyridyl)*

A solution of β-nicotinylpropionic acid (15) (2.00 g, 11.2 mmol) in 15 ml of water containing sodium hydroxide (20 mmol) was added dropwise to a stirred ice-cold solution of sodium borohydride (400 mg, 10.8 mmol) in 20 ml of 0.2 *N* sodium hydroxide under nitrogen. Stirring was continued at room temperature for 22 h, and the cooled reaction mixture was neutralized with concentrated sulfuric acid. A further 10 ml of concentrated sulfuric acid was added and the solution was stirred at room temperature for 22 h. The solution was made basic with solid sodium carbonate and extracted with methylene chloride. The extract afforded the lactone **15** (R = 3-pyridyl) in 13% yield as a colorless oil which was suitable for the next step. An analytical sample was purified by microdistillation. *Anal.* calcd. for $C_9H_9NO_2$: C 66.24, H 5.56, N 8.58; found: C 66.02, H 5.65, N 8.46. Spectroscopic characteristics: ir 5.60; uv 211 (6600), 255 (6200), 260 (6900), 266 (4950); nmr 1.23–2.80 (m, 4H), 4.47 ('t', 7 Hz spacings, 1H), 7.0–8.1 (m, 4H); ms 164 (19), 163 (100), 162 (29), 135 (35), 134 (90), 119 (24), 118 (50), 109 (17), 108 (60), 107 (25), 106 (63).

A solution of the pyridylbutyrolactone **15** (R = 3-pyridyl) (198 mg, 1.21 mmol) and tryptamine (198 mg, 1.24 mmol) in 0.5 ml of absolute ethanol was refluxed for 15 h under nitrogen. The solvent was removed on a rotary evaporator, and the oily product was subjected to preparative tlc with m-m-a elution. The tryptamide **14** (R = 3-pyridyl) was obtained as an uncrystallizable colorless gum (206 mg, 0.64 mmol). An analytical sample was prepared by microdistillation. *Anal.* calcd. for $C_{19}H_{21}N_3O_2$: C 70.56, H 6.55, N 13.00; found: C 70.00, H 6.74, N 12.67. Spectroscopic characteristics: ir 2.89, 3.03, 6.05; ms 323 (1), 305 (2), 164 (9) 163 (70), 162 (18), 160 (22), 134 (39), 131 (60), 130 (100), 120 (28), 108 (72), 107 (15), 106 (30).

The hydroxytryptamide **14** (R = 3-pyridyl) (170 mg) was acetylated in the manner described above for **14** (R = Ph). The acetate was recovered in 95% yield as an uncrystallizable colorless gum: ir 2.87, 3.0, 5.79, 6.01; uv 225 (22 900), 262 (5050), 268 (5300), 282 (4700), 291 (3950); nmr 0.73 (br, 1H, removed by $NaOD/D_2O$), 1.3–3.2 (complex, 8H), 3.80 ('t', 6 Hz spacings, 1H, removed by $NaOD/D_2O$), 4.30 (m, 1H), 6.48 (4 peaks, 6 Hz spacings, 2H, after $NaOD/D_2O$ treatment, 3 peaks, 6 Hz spacings, 2H), 7.10 (3 peaks, 6 Hz spacings, 2H), 7.7–8.2 (m, 4H), 8.00 (s, 3H); ms 366 (4), 365 (14), 305 (5), 223 (15), 164 (6), 163 (9), 144 (17), 143 (100), 131 (6), 130 (40).

The acetylated product (169 mg, 0.46 mmol) was treated with 5 ml of phosphorus oxychloride in the manner described above. The product was obtained as a yellow glassy solid (132 mg, 0.38 mmol): ir 2.89, 3.06, 5.80; uv 214 (23 400), 317 (11 700); in MeOH–HCl 212 (17 700), 250 (11 200), 356 (16 700); nmr −0.37 (br, 1H), 1.4–3.0 (complex, 8H), 3.9–4.3 (m, 1H), 5.9–6.3 (m, 2H), 6.8–8.2 (complex, 6H), 8.03 (s, 3H); ms 348 (4), 347 (12),

289 (65), 288 (54), 287 (52), 286 (50), 211 (20), 210 (100), 209 (19), 168 (100), 167 (40); high resolution ms 347.1634 ($C_{21}H_{21}N_3O_2$: 347.1634).

This acetate (120 mg, 0.37 mmol) was hydrolyzed in the manner described in the preparation of **13** (R = Ph). The product, **13** (R = 3-pyridyl), was recovered as an uncrystallizable glassy yellow solid (103 mg, 0.34 mmol): ir 2.89, 3.12; uv 213 (17 600), 239 (12 700), 243 (12 600), 260 (sh), 268 (sh), 319 (12 000), in MeOH–HCl 213 (17 600), 250 (10 100), 356 (18 100); in MeOH–KOH 213 (22 300), 239 (14 500), 243 (14 300), 260 (sh), 268 (sh), 318 (13 400); nmr ($CDCl_3$/DMSO-d_6) −1.27 (br, 1H), 1.2–3.0 (complex, 8H), 4.8–5.2 (m, 2H), 5.9–6.3 (m, 2H), 6.8–7.5 (m, 4H), 7.6–8.0 (m, 2H).

*Naucleonine, **19**, and Naucleonidine, **20***

*Model compound **18** (R = H)*

A solution of harmalan, **16**, (364 mg, 2 mmol) and 0.5 ml of freshly distilled ethylene bromohydrin (8 mmol) in 8 ml of dry chloroform was refluxed under nitrogen for 16 h. The yellow solid which precipitated was collected, washed with chloroform, and recrystallized from ethanol – ethyl acetate. The hydrobromide **17** (R = H) was obtained as yellow needles (115 mg, 0.37 mmol), mp 233–240 °C (dec.). *Anal.* calcd. for $C_{14}H_{17}N_2OBr$: C 54.38, H 5.54, N 9.06, Br 25.84; found: C 54.57, H 5.78, N 9.04, Br 25.83. Spectroscopic characteristics: ir (Nujol) 3.04, 3.23, 6.18, 6.25, 6.38, 6.46; uv 210 (14 600), 249 (9100), 358 (17 000).

The hydrobromide (114 mg, 0.37 mmol) was suspended in a rapidly stirred mixture of 30 ml of methylene chloride and 30 ml of 5% aqueous potassium hydroxide under nitrogen and the stirring was continued for 1 h. The phases were separated and the aqueous phase was extracted with two 50 ml portions of methylene chloride. The combined organic phases yielded the oxazolidine **18** (R = H) as a pale yellow glass (74 mg, 0.33 mmol): ir 2.90, 3.05; uv 226 (15 300), 248 (6100), 275 (2300), 283 (2400), 291 (2600), 357 (10 000); in MeOH–HCl 211 (14 000), 249 (9700), 357 (20 800); in MeOH–KOH 226 (23 300), 275 (6800), 282 (7000), 291 (5300); nmr 1.01 (s, 1H), 2.3–3.0 (m, 4H), 5.7–6.4 (m, 2H), 6.5–7.8 (complex, 2H), 8.28 (s, 3H, removed by D_2O).

*Model compound **18** (R = Ph)*

A solution of harmalan, **16**, (166 mg, 0.9 mmol) and styrene oxide (233 mg, 1.9 mmol) in 8 ml of chloroform was refluxed under nitrogen for 5 days. Removal of the solvent afforded a yellow oil which was purified by preparative tlc with m-m-a elution. The oxazolidine **18** (R = Ph) was obtained as an oil (166 mg, 0.55 mmol): ir 2.90, 3.04; uv 225 (20 600), 250 (6200), 274 (3800), 282 (3800), 291 (3300), 360 (11 400); in MeOH–HCl 214 (16 600), 250 (10 400), 362 (23 500); in MeOH–KOH 229 (24 900), 275 (8300), 282 (8300), 291 (7100); nmr (areas based on 50:50 mixture of two $C_{20}H_{20}N_2O$ isomers) 1.36 (s, 1H, removed by D_2O), 1.53 (s, 1H, removed by D_2O), 2.4–3.0 (complex, 18H), 4.66 (4 peaks, separations 6, 4, 6 Hz, 1H), 5.12 (4 peaks, separations 6, 1, 6 Hz, 1H), 6.4–7.6 (complex, 12H), 8.21 (s, 3H, removed by D_2O), 8.26 (s, 3H, removed by D_2O); ms 305 (5), 304 (14), 290 (20), 289 (100), 200 (5), 199 (13), 198 (57), 197 (12), 185 (6), 184 (6), 183 (12), 182 (6), 172 (15), 171 (7), 170 (12).

A sample of the picrate, mp 215–230 °C (dec.), was prepared for analysis. *Anal.* calcd. for $C_{26}H_{23}N_5O_8$: C 58.53, H 4.35, N 13.13; found: C 58.48, H 4.17, N 12.88.

*Naucleonine, **19***

Sodium hydride (1.8 g of a 57% dispersion in mineral oil, 43 mmol) was washed with hexane to remove the mineral oil, and then suspended in 30 ml of dry dimethyl sulfoxide stirred under nitrogen. Trimethyloxosulfonium iodide (9.2 g, 42 mmol) was added to the stirred suspension and, when evolution of hydrogen had ceased, a solution of 3-pyridinecarboxaldehyde (3.51 g, 33 mmol) in 20 ml of dimethyl sulfoxide was added dropwise over 15 min. The mixture was heated in an oil bath at 53 °C for 30 min, cooled, and poured into 500 ml of ice water. Extraction with methylene chloride afforded 3-vinylpyridine epoxide as a pale yellow oil (3.72 g) which darkened rapidly on standing. Attempts to purify the epoxide further were unsuccessful because of its instability.

The freshly prepared epoxide (117 mg, 0.97 mmol) and harmalan, **16**, (145 mg, 0.8 mmol) were heated together at 50 °C under nitrogen for 18.5 h. Preparative tlc of the crude reaction mixture with elution by methanol yielded a glassy solid (77 mg, 0.25 mmol) which had the same tlc behavior as natural naucleonine (ND-305B) and very similar spectroscopic characteristics (1*b*). The synthetic naucleonine, **19**, could not be obtained in a crystalline form, but further purification was carried out by tlc with m-m-a elution. *Anal.* calcd. for $C_{19}H_{19}N_3O$: C 74.73, H 6.27, N 13.76; found: C 74.77, H 6.15, N 13.28. Spectroscopic characteristics: ir 2.90 (sharp), 3.1; uv 224 (21 300), 252 (7600), 268 (5400), 281 (4000), 291 (3200), 360 (10 500); in MeOH–HCl 213 (16 500), 251 (11 900), 363 (23 800); in MeOH–KOH 227 (29 700), 269 (8700), 282 (7600), 291 (6400), nmr (areas based on equimolar mixture of **19***a* and **19***b*) 0.96 (s, 1H, removed by D_2O), 1.00 (s, 1H, removed by D_2O), 1.3–2.5 (complex, 8H), 2.5–3.0 (complex, 8H), 4.71 (4 peaks, spacings 6, 3, and 6 Hz, 1H), 5.10 (4 peaks, spacings 6, 1, and 6 Hz, 1H), 6.1–7.6 (complex, 12H), 8.21 (s, 3H, removed by D_2O), 8.24 (s, 3H, removed by D_2O); ms 306 (5), 305 (18), 291 (22), 290 (100), 199 (3), 198 (14), 197 (3), 184 (5), 183 (6), 172 (5), 156 (3), 155 (5), 154 (4), 144 (5), 143 (3), 130 (4), 129 (2), 128 (2), 115 (2), 107 (4), 106 (8), 78 (4), 77 (2); high resolution ms 305.1530 ($C_{19}H_{19}N_3O$: 305.1528).

*Naucleonidine, **20***

A solution of the epoxide of 3-vinyl-5-carbomethoxy pyridine, **11**, (described above) (394 mg, 2.20 mmol) and harmalan, **16**, (377 mg, 2.05 mmol) in 5 ml of chloroform was refluxed under nitrogen for 72 h. Solvent was removed on a rotary evaporator and the brown gum that remained was subjected to tlc with m-m-a elution. A glassy solid (355 mg, 0.98 mmol) was obtained that had the same tlc behavior as naucleonidine (ND-363C) and very similar spectroscopic characteristics (1*b*). The synthetic naucleonidine, **20**, could not be obtained in crystalline form, but further purification was carried out by tlc with m-m-a elution. *Anal.* calcd. for $C_{21}H_{21}N_3O_3$: C 69.40, H 5.83, N 11.56; found: C 69.29, H 5.79, N 11.26. Spectroscopic characteristics: ir 2.90 (sharp), 3.05, 5.80, 5.82 (sh); uv 224 (28 200), 272 (6650), 291 (4450), 360 (5850); in MeOH–HCl 212 (18 950), 250 (10 900), 364 (21 200); in MeOH–KOH 225 (35 100), 273 (10 000), 291 (7250);

nmr (areas based on equimolar mixture of **20***a* and **20***b*) 0.86 (superimposed signals, 3H, after D_2O treatment, d, J = 2 Hz, 1H), 1.02 (d, J = 2 Hz, 1H), 1.21 (d, J = 2 Hz, 1H), 1.52 (d, J = 2 Hz, 1H), 1.68 ('t', 2 Hz spacings, 1H), 2.20 ('t', 2 Hz spacings, 1H), 2.4–3.0 (complex, 8H), 4.71 (4 peaks, spacings 6, 3, and 6 Hz, 1H), 5.09 (4 peaks, spacings 6, 1, and 6 Hz, 1H), 6.10 (s, 3H), 6.34 (s, 3H), 6.3–7.5 (complex, 12H), 8.22 (s, 6H, removed by D_2O); ms 364 (7), 363 (19), 349 (26), 348 (100), 332 (2), 316 (5), 199 (8), 198 (25), 197 (6), 183 (6), 172 (10), 170 (6), 169 (6), 165 (9), 164 (14), 157 (5), 156 (5), 155 (9), 154 (7), 144 (10), 143 (5), 134 (9), 130 (9), 129 (7), 128 (4), 115 (4), 106 (5), 104 (5), 99 (6), 77 (6); high resolution ms 363.1585 ($C_{21}H_{21}N_3O_3$: 363.1582).

Alkaloid ND-363B

This substance was obtained as a syrup in the tlc fractionation of the *N. diderrichii* extract (1*a*, *b*): ir 2.90 (sharp), 3.1 (br), 5.80, 5.82 (sh); uv (extinction coefficients based on mol. wt. 738) 222 (60 400), 270 (13 850), 279 (sh), 289 (sh), 361 (8300); in MeOH–HCl 222 (end absorption 29 000), 247 (19 600), 265 (sh), 362 (35 600); in MeOH–KOH 223 (71 000), 273 (15 500), 280 (sh), 289 (sh); nmr (integrated areas uncertain, comparison made with naucleonidine (ND-363C) spectrum (1*b*) and comment made only on significant differences) 0.75–2.2 (peaks correspond, but each broadened or doubled, peak at 0.96 removed by D_2O), 4.76 (4 peaks, each split further), 5.03 (3 peaks, each split further), 6.04 (s), 6.08 (s), 6.25 (s), 6.27 (s), 7.9 (broad peak, absent in ND-363C; removed by D_2O; no peak near 8.2); ms 364 (7), 363 (20), 362 (4), 349 (25), 348 (100), 332 (3), 316 (4), 279 (5), 199 (13), 198 (27); metastables 334.0 (calcd. for 363 → 348: 333.6), 287.1 (calcd. for 348 → 316: 286.9); high resolution ms 363.1581 ($C_{21}H_{21}N_3O_3$: 363.1582), 348.1354 ($C_{20}H_{18}N_3O_3$: 348.1348), 316.1089 ($C_{19}H_{14}N_3O_2$: 316.1086); field desorption ms (low temperature) 741 (17), 739 (7), 376 (22), 364 (100), 278 (10); (high temperature) 376 (10), 364 (100), 182 (22), 166 (38).

Dihydrocadambine, **22**

This alkaloid was isolated as a pale brown glass in the tlc fractionation of the *N. diderrichii* extract (1*a*, *b*): ir 2.92 (sh), 3.05 (br, strong), 5.93, 6.12; uv 225 (27 550), 278 (6300); nmr tabulated previously (2*a*); field desorption ms 546. Acetylation with acetic anhydride and pyridine at room temperature and purification by tlc with elution by 96:4 chloroform–methanol provided a syrup: ir 2.89 (sharp), 3.02 (br, medium height), 5.73 (strong), 5.89, 6.10; nmr tabulated previously (2*a*); field desorption ms 756. *Anal.* calcd. for $C_{37}H_{44}N_2O_{15}$: C 58.72, H 5.86, N 3.71, 5Ac 28.48, for $C_{37}H_{44}N_2O_{15}\cdot CH_3OH$: C 57.86, H 6.13, N 3.55, 5Ac 27.29; found: C 57.74, H 6.43, N 3.43, Ac 26.83.

Acknowledgments

This paper is taken from the Ph.D. theses (University of Toronto, 1974) of G.I.D. and A.S. We thank the National Research Council of Canada for support of this investigation and for a scholarship (to G.I.D.). We thank Professor G. W. Wood, University of Windsor, for the field desorption mass spectra.

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