SOME ASPECTS OF THE CHEMISTRY OF CATHARANTHINE AND CLEAVAMINE

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Received November 13, 1964

Dedicated to Professor R. B. Sandin on the Occasion of his Sixty-Eighth Birthday

ABSTRACT

Chemical and spectroscopic evidence is presented for an interesting acid-catalyzed rearrangement of the alkaloid catharanthine. Four reaction products (descarbomethoxycatharanthine and cleavamine and its two dihydro derivatives) were isolated, and their formation is rationalized by a mechanism involving ring-opened intermediates. Evidence is presented in support of the proposed mechanism and, in particular, a novel transannular cyclization leading to the *Iboga* alkaloid skeleton is shown in support of the steps postulated for the formation of descarbomethoxycatharanthine.

The X-ray analysis of cleavamine methiodide established the absolute configuration of the lone asymmetric center present in the molecule and, from these results, the absolute configuration of the *Iboga* alkaloids can be derived.

During investigations by the Lilly group (1) on the dimeric *Vinca* alkaloids (vincaleukoblastine (VLB), leurosine, and leurocristine), it was found that each was cleaved by concentrated hydrochloric acid to an indole compound and vindoline derivative. The vindoline derivative of VLB and leurosine was desacetylvindoline (I), whereas leurocristine gave des-$N_{(a)}$-methyl-desacetylvindoline (II). Both VLB and leurocristine afforded the same indole derivative, velbanamine, $C_{19}H_{26}N_2O$, but the corresponding compound with leurosine was called cleavamine, $C_{19}H_{24}N_2$.

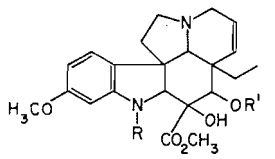
In the same communication it was also reported that the known alkaloid catharanthine (III (2)), when subjected to the same acid treatment, also provided cleavamine as one of the reaction products. The suggestion that cleavamine possessed a tetracyclic structure similar to the known *Aspidosperma* alkaloid quebrachamine (3) stimulated further research in our laboratory to establish conclusively the structure and stereochemistry of this substance. At the outset we felt that this investigation might not only provide indirect evidence for the presence of a catharanthine-like unit in the biologically important VLB molecule, but also illustrate a novel acid-catalyzed rearrangement in the *Iboga* alkaloid series. Furthermore, if the absolute configuration of the asymmetric center in the molecule could be established, it would provide indisputable evidence for the absolute configuration of the *Iboga* alkaloids.

With this view in mind, we initiated a detailed study of the catharanthine–cleavamine transformation and some of our results concerning the structure of cleavamine have already been published (4). Fortunately, the X-ray analysis of cleavamine methiodide established the structure and absolute configuration at C-2[1] as depicted in IV. We now wish to discuss these results in some detail and to present more recent evidence which is relevant to the mechanism of this interesting transformation.

Before considering mechanism, we wish to discuss briefly the stereochemistry of the *Iboga* alkaloids, since, in conjunction with the results of other workers and the evidence presented herein, it is possible to assign the absolute configuration for this series of

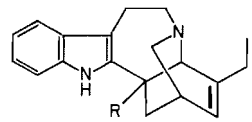
[1]*The numbering system used here is that of the Iboga alkaloids (see ref. 7).*

alkaloids. It is obvious that the absolute configuration of C-2 in IV immediately reveals the absolute configuration of this carbon atom in the catharanthine molecule, since there is little reason to suspect that any configurational change would occur in the catharanthine–cleavamine conversion. However, even this vague possibility has been eliminated in our recent transannular cyclization studies (5) wherein a cleavamine derivative has been converted to dihydrocatharanthine and the *Iboga* alkaloid, coronaridine. These results establish that the same stereochemistry at C-2 prevails in the rigid *Iboga* structure as in the relatively nonrigid cleavamine molecule. Since a previous X-ray study on ibogaine hydrobromide (6) had already established a *cis* relationship between the ethyl group at C-4 and the $\rangle$N—C-19 bridge, it is clear that the absolute configuration at C-4 and, in turn, for the entire *Iboga* alkaloid system is now established as shown in V for ibogamine.



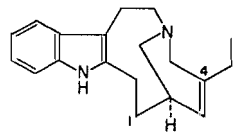
(I) R = CH_3; R' = H

(II) R = H; R' = H



(III) R = $COOCH_3$

(VI) R = H



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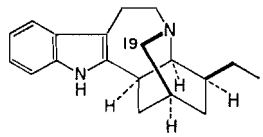
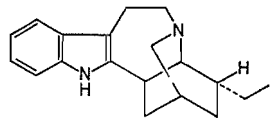
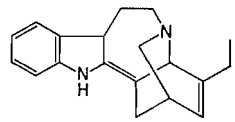


(V)



(VII)



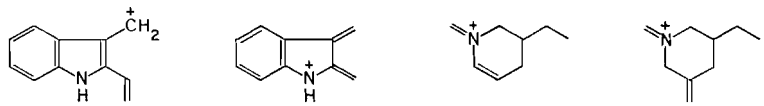
(VIII)

It should be noted that in their elegant work on the alkaloids of *Tabernanthe iboga*, the Ciba group (7) had previously postulated that the ethyl group at C-4 was *trans* to the $\rangle$N—C-19 bridge. Furthermore, these workers had compared the optical rotatory dispersion curve for one of their bicyclic degradation products with a decalin derivative of established configuration and on this basis suggested an absolute stereochemistry for this group of alkaloids. It is pleasing to note that, with the exception of the incorrect assignment at C-4, the remaining stereochemical centers were proposed as in V. Consequently, in this instance, the optical comparison of a piperidone ring with a cyclohexanone system has now been proved as valid, although some reservations about this point were understandably expressed at that time.

Turning to the mechanistic interpretation of the acid-catalyzed rearrangement of catharanthine, we felt that we should carry out a more detailed investigation of this reaction in an attempt to isolate as many products as possible, since these may provide evidence as to the nature of this rearrangement. Apart from the isolation of cleavamine, another product, descarbomethoxycatharanthine (VI), had been previously obtained from this reaction (8) but, since the combined yield of these two products constituted only about 20% of the total reaction mixture, we decided to examine this mixture more closely.

The cleavamine mother liquors and several cleavamine-containing fractions were combined and subjected to several very careful column chromatographic separations. Apart from the many fractions containing intractable gums and resins, one fraction which could be well characterized was obtained. It is appropriate to discuss this in some detail, since additional evidence which was germane to any mechanistic interpretation was furnished.

This fraction, designated as B9, was a mixture of two compounds, as shown by thin-layer chromatography, but numerous attempts to completely separate these compounds by various techniques failed. Consequently, we will discuss the spectral data obtained on B9 and show how the results led to the characterization of these two compounds as the two possible dihydrocleavamines epimeric at C-4. No olefinic protons were apparent in the nuclear magnetic resonance spectrum of B9, and the methyl triplet normally present at 8.96 τ in cleavamine had shifted to 9.13 τ. The mass spectrum showed a molecular ion at *m/e* 282, and other significant peaks at *m/e* 156, 143, 138, and 124 could be attributed to the following fragments, which are given by 4β-dihydrocleavamine (4, 10).[2]



m/e 156 143 124 138

In general, the mass spectrum of B9 was practically superimposable on that of 4β-dihydrocleavamine, and also the infrared spectra were similar. The leading spot of the mixture had the same R_f value as 4β-dihydrocleavamine on thin-layer chromatography, and the second spot was thought to be due to a dihydrocleavamine epimeric at C-4, which we designated as 4α-dihydrocleavamine. Fortunately, from other studies at the Lilly laboratories, a C-4 epimer of 4β-dihydrocleavamine had been isolated and we were able to demonstrate that this compound was identical with our sample of 4α-dihydrocleavamine. A synthetic mixture of the dihydrocleavamines duplicated the behavior of fraction B9 on thin-layer chromatography and gave an identical infrared spectrum.

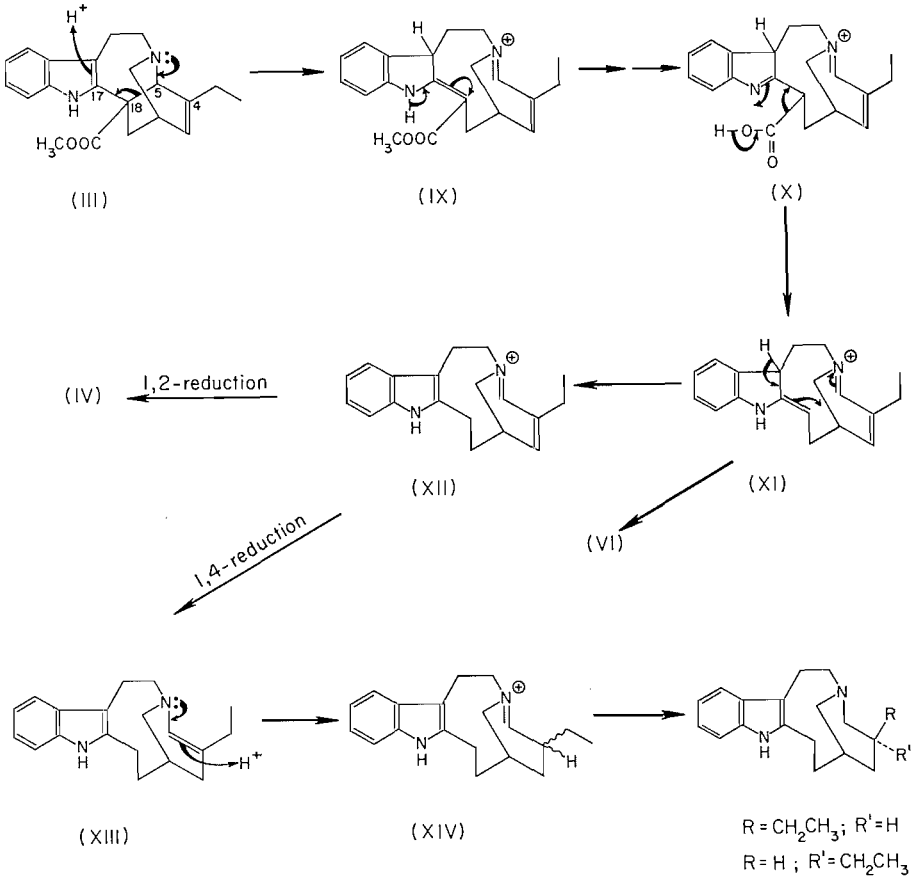
Two dihydro derivatives epimeric at C-4 could, in theory, arise from an acid-catalyzed rearrangement of dihydrocatharanthine, formed by the reduction of catharanthine during the course of the reaction, or they could arise from the reduction of cleavamine itself. The former possibility is eliminated, since it is well known (8) that dihydrocatharanthine does not yield any tetracyclic products under the reaction conditions utilized above, whereas we have recently shown that cleavamine is not reduced to the dihydro derivatives under these conditions as well. This evidence indicates that these dihydro compounds arise from a ring-opened intermediate which can lead to cleavamine on the one hand and to dihydrocleavamines on the other.

Perhaps the most interesting aspect of the acid reaction on catharanthine comes forth from consideration of the formation of descarbomethoxycatharanthine. Some earlier work by the Lilly group (8) established that, although dihydrocatharanthine, like its relatives in the *Iboga* series (7, 11, 12), decarboxylated readily to yield the corresponding descarbomethoxy base, epi-ibogamine (VII), catharanthine did not undergo an analogous transformation under these conditions. Although this may seem somewhat puzzling,

[2]*In a related investigation to be reported later, we have shown by the X-ray analysis technique that dihydrocleavamine prepared by catalytic reduction of cleavamine has the ethyl group at C-4 in the β-configuration and is therefore referred to as 4β-dihydrocleavamine. The C-4 epimer obtained from decarbomethoxylation of carbomethoxydihydrocleavamine is therefore 4α-dihydrocleavamine.*

there is a very reasonable rationalization for this difference in reaction. Consideration of the accepted decarboxylation mechanisms (7, 12) for these compounds leads to the realization that in the case of catharanthine an intermediate of type VIII becomes necessary. Molecular models reveal that this intermediate would be very highly strained and there is serious doubt whether it can exist at all. On the other hand, the corresponding intermediate in the reduced series can form easily and it is felt that this accounts for the marked difference in reactivity toward the decarboxylation reaction. Therefore, the formation of descarbomethoxycatharanthine does not involve a simple decarboxylation but must be explained in some other manner.

In relation to some transannular cyclization studies in our laboratory, some of which have been recently published (5, 13, 14), it was extremely attractive to consider that the formation of all the products which have been isolated from the reaction of catharanthine with concentrated hydrochloric acid can be rationalized on the basis of the mechanism shown in Reaction Scheme 1.



REACTION SCHEME 1.

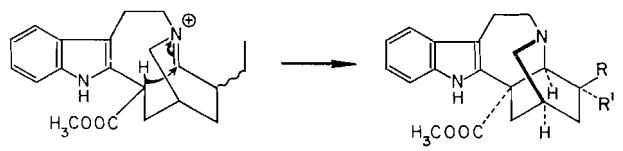
The lone pair of electrons on $N_{(b)}$ in III can participate in a rearrangement to form an iminium ion, with concurrent ring cleavage and protonation at the β-position of the indole. The resulting ring-opened intermediate IX is stabilized by two factors: (i) the

conjugated nature of the iminium ion, and (ii) the conjugation of the newly generated double bond between C-17 and C-18 with both the ester and anilino functions. After acid hydrolysis of the ester, decarboxylation may occur via X in a manner analogous to the mechanism proposed for the *Iboga* alkaloids (7, 12). This ring-opened intermediate renders the molecule more flexible and the decarboxylated intermediate XI is obtained, whereas, as already mentioned above, the cyclic intermediate VIII necessary for decarboxylation of the rigid catharanthine molecule is highly strained.

The crucial intermediate XI may follow either of two reaction paths. If the original electron flow is reversed, then the C-5/C-18 bond is regenerated and the product is descarbomethoxycatharanthine (VI). But if the α-methylene indoline system in XI merely rearranges to the indole, the intermediate XII from which the ring-opened tetracyclic compounds must ultimately be formed is obtained. If one assumes that XII is the actual intermediate, 1,2-reduction of the iminium ion will give cleavamine directly. On the other hand, 1,4-reduction can also occur to afford an enamine, XIII, which rearranges in the well-known manner to the iminium compound XIV, with subsequent reduction to provide the two isomeric dihydrocleavamines. A mixture of 4α- and 4β-dihydrocleavamines is obtained, because the approach of the proton to C-4 in XIII can occur from above or below the plane of the ring with equal facility.

A mechanism involving tetracyclic intermediates has also been proposed by the Lilly group to explain some of their results (8), although their detailed mechanistic interpretation still remains to be published.[3]

We wish now to present additional evidence to the results already mentioned above, which we feel provide substantial support for the mechanistic speculations. One of the crucial steps in the mechanism implies a transannular cyclization of intermediate XI to provide a route to descarbomethoxycatharanthine. We have recently demonstrated (5) that this interesting reaction can indeed occur quite easily and does provide the *Iboga* alkaloid skeleton. These results can be summarized by the sequence shown in Reaction Scheme 2.



(XV) R = CH_2CH_3; R' = H

(XVI) R = H; R' = CH_2CH_3

REACTION SCHEME 2.

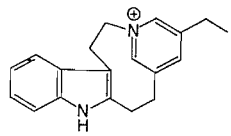
The isolation of coronaridine (XV) and dihydrocatharanthine (XVI) in this reaction (5) is of considerable interest to the mechanism postulated above. First of all, it provides reasonable evidence for the feasibility of the process XI → VI. Secondly, it also shows that epimerization at C-4, as suggested to explain the isolation of the two dihydrocleavamines, can and does proceed through an iminium–enamine equilibrium. We feel that these results add considerable strength to the postulates mentioned above.

We also wish to point out that it is not possible to ascertain, from the evidence presented herein, exactly when the loss of the ester group occurs, although the sequence

[3]*After our paper had been submitted for publication, a detailed account of this work appeared (9).*

suggested by IX → XI seems most reasonable at this time. It is pertinent to note that the recent isolation of carbomethoxydihydrocleavamine from the reduction of catharanthine with zinc in acetic acid (15) provides evidence that the reduction of the iminium system can occur before the loss of the ester group.

Finally, it is important to emphasize that the last steps of the above mechanism explain the formation of cleavamine and its dihydro derivatives when catharanthine is reacted with acid in the presence of a reducing agent (stannous chloride, mossy tin). Since it has been established (8) that cleavamine is also formed (although in lower yield) by the action of concentrated hydrochloric acid alone, one must account for its formation under these conditions. In the absence of an inorganic reducing agent, the reduction step possibly takes place via an intramolecular redox reaction wherein two molecules of the intermediate XII react to yield one molecule of cleavamine and one of a pyridinium compound XVII. The increase in yield of cleavamine in a reducing medium is thus explicable on the grounds that XII is reduced directly to cleavamine and no pyridinium compound is formed.



(XVII)

The acid-catalyzed rearrangement of catharanthine to the ring-opened intermediates is an interesting conversion both from a mechanistic and a biosynthetic standpoint. Some related aspects of this reaction are under study in our laboratory at present.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet spectra were measured in methanol solution on a Cary 14 spectrophotometer and infrared spectra were taken on a Perkin–Elmer model 21 spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were recorded at 60 Mc/s on a Varian A60 instrument. The line positions or centers of multiplets are given in the Tiers τ scale with reference to tetramethylsilane as the internal standard, with the multiplicity, integrated areas, and types of protons being indicated in parentheses. Silica gel G plates were used for thin-layer chromatography (t.l.c.) and were developed by ethyl acetate, or ethyl acetate – chloroform mixtures as given below. The alumina used for column chromatography was Shawinigan reagent, deactivated with 3% of 10% aqueous acetic acid unless otherwise stated. Analyses were performed by the Microanalytical Laboratory, University of British Columbia, and by Dr. A. Bernhardt and his associates, Mulheim (Ruhr), Germany. All molecular weights were determined by mass spectrometry on an Atlas CH4 spectrometer.

Reaction of Catharanthine with Concentrated Hydrochloric Acid

(a) Isolation of Cleavamine and Descarbomethoxycatharanthine

The procedure indicated here is somewhat modified from that originally developed in the Lilly Research Laboratories.

A mixture of catharanthine hydrochloride (40 g), stannous chloride (44 g), and mossy tin (4 g) in concentrated hydrochloric acid (520 ml) was heated under reflux in a nitrogen atmosphere for 75 min. By the end of this time an orange-red gum had formed in the reaction mixture. The acidic solution was decanted from the gum and washed with methylene chloride (3 × 100 ml). The washings were combined with the gum, and then methanol (50 ml) and methylene chloride (100 ml) were added so that a clear solution was obtained. This solution was shaken with 1 *N* aqueous sodium hydroxide (600 ml), separated, and washed with water (200 ml). The sodium hydroxide solution was washed with ether (2 × 100 ml) and the ethereal extract added to the methylene chloride solution. After it was dried over magnesium sulfate, the organic solution was evaporated to leave a reddish oil (32 g), which was taken up in benzene and chromatographed on alumina (1 200 g).

Cleavamine was eluted in the initial benzene – petroleum ether (b.p. 30–60°, 1:1) fractions and recrystallized from methanol to give needles (2.4 g), m.p. 117–119°; one spot of t.l.c. (ethyl acetate); $[\alpha]_D^{26}$ + 73° ($CHCl_3$); λ_{max} (log ϵ): 228 (4.60), 285 (3.87), 292 (3.86) mμ; ν_{max}^{Nujol}: 3 420 (NH), 2 800, 2 740, 2 700 cm^{-1} (Bohlmann bands) (16), no carbonyl absorption; n.m.r. signals (CD_3COCD_3): 0.87 (singlet, 1H, NH), 2.8 (multiplet, 4H, aromatic), 4.72 (doublet, 1H, olefinic), 8.96 τ (triplet, 3H, CH_2CH_3).

Anal. Found: C, 81.30; H, 8.54; N, 10.18; mol. wt. 280. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99; mol. wt. 280.

Cleavamine methiodide was formed by merely adding an excess of methyl iodide to a methanol solution of cleavamine and allowing the mixture to stand overnight in a refrigerator. The analytical sample was prepared by recrystallizing it from a mixture of methanol – ethyl ether – petroleum ether, m.p. 244–245° (decomp.). This derivative was used for the X-ray analysis (4).

Anal. Found: C, 56.83; H, 6.46; N, 6.63. Calcd. for $C_{20}H_{24}N_2I$: C, 56.87; H, 6.46; N, 6.45.

The sample of cleavamine was identical in every respect with an authentic sample kindly provided by Dr. M. Gorman, Eli Lilly and Company.

Benzene–chloroform (1:1) elution provided unreacted starting material (7 g) in the initial fractions and descarbomethoxycatharanthine (1.0 g) in the later fractions. The latter material was recrystallized twice from ether to yield needles, m.p. 103–104°.

Anal. Found: C, 81.70; H, 8.12; N, 10.10. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06.

This material was subsequently shown to be identical in every respect with an authentic sample of descarbomethoxycatharanthine kindly provided by Dr. M. Gorman, Eli Lilly and Company.

(b) Isolation of 4α- and 4β-Dihydrocleavamines (Fraction B9)

The later benzene – petroleum ether (1:1) fractions, after the major cleavamine-containing fractions had been removed in the above chromatography, displayed three spots on t.l.c. (ethyl acetate) with R_f values of 0.77, 0.53, and 0.27. The compound with a R_f value of 0.77 was found to correspond to cleavamine. These fractions were combined (5.4 g) and placed on another alumina column (450 g). Elution was begun with benzene – petroleum ether (1:2) and the first four fractions afforded cleavamine (1.4 g) after recrystallization from methanol. The later fractions contained progressively less cleavamine and more of the other two constituents. The last (B9, 55 mg) of the nine fractions obtained with this eluent contained no cleavamine and displayed only two spots on t.l.c. Recrystallization from aqueous ethanol gave light brown prisms, m.p. 127–132°; ν_{max}^{Nujol}: 3 410 (NH), 2 790, 2 740 cm^{-1} (Bohlmann bands); n.m.r. ($CDCl_3$): 2.8 (multiplet, 4H, aromatic), 9.13 τ (broad, 3H, CH_2CH_3), no olefinic proton signals.

Anal. Found: C, 80.56; H, 9.46; N, 10.04; mol. wt. 282. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; mol. wt. 282.

Fraction B9 was shown to be a mixture of 4α- and 4β-dihydrocleavamines by comparison (t.l.c. and infrared and mass spectra) with authentic samples as prepared below.

4β-Dihydrocleavamine

Cleavamine (1.5 g) in ethyl acetate (20 ml) was hydrogenated over Adam's catalyst (150 mg). Uptake of hydrogen ceased after 50 min, at which time 1 mole of hydrogen had been absorbed. Filtration and evaporation of the solvent gave 4β-dihydrocleavamine, which recrystallized from methanol as prisms (1.2 g), m.p. 136–138°; one spot on t.l.c. (ethyl acetate); ν_{max}^{Nujol}: 3 410 (NH), 2 790, 2 750 cm^{-1} (Bohlmann bands); n.m.r. (CD_3COCD_3): 0.88 (singlet, 1H, NH), 2.8 (multiplet, 4H, aromatic), 9.17 τ (triplet, 3H, CH_2CH_3).

Anal. Found: C, 81.02; H, 9.59; N, 9.88; mol. wt. 282. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; mol. wt. 282.

4α-Dihydrocleavamine

Carbomethoxydihydrocleavamine (15) (500 mg) in 5 *N* hydrochloric acid (30 ml) was heated on the water bath under a nitrogen atmosphere for 8 h. The solution was cooled in ice, made basic with aqueous ammonia, and extracted with methylene chloride (3 × 50 ml). The organic extract was dried, concentrated to a small volume, and filtered through alumina (10g). Evaporation of the solvent gave an amorphous powder (340 mg) which could not be induced to crystallize. In spite of its amorphous nature it showed only one spot on t.l.c. (ethyl acetate); ν_{max}^{Nujol}: 3 350 (NH), 2 750 cm^{-1}, no carbonyl absorption.

This material was subsequently shown to be identical (t.l.c. and infrared spectra) with an authentic sample of a 4-dihydrocleavamine isomer kindly supplied by Dr. M. Gorman, Eli Lilly and Company. We have now shown[2] that this isomer must have the ethyl group in the α-configuration, and therefore carbomethoxydihydrocleavamine is in the 4α series as well.

Mercuric Acetate Oxidation of Carbomethoxydihydrocleavamine

Carbomethoxydihydrocleavamine (4.5 g) and mercuric acetate (10.5 g) in glacial acetic acid (150 ml) were stirred under a nitrogen atmosphere for 40 h. The solution was then filtered from the precipitated mercurous acetate (8.2 g) and heated under reflux for 5 h. The solvent was removed as far as possible under vacuum, and the residue made basic with dilute ammonia (50 ml) and extracted with methylene chloride (3 × 50 ml).

After the solution was dried over sodium sulfate, the methylene chloride was removed, and the dark brown product chromatographed on alumina (200 g, deactivated with 0.6 ml of glacial acetic acid). The

initial benzene fractions afforded a vincadifformine-like product as a white powder (1.15 g). Although the structure of this material has been fully established (14), it bears no direct relevance to the present paper and a more detailed discussion of its chemistry will be presented in a later paper.

The later benzene fractions yielded an amorphous powder (450 mg); one spot on t.l.c. (ethyl acetate – chloroform, 1:9); λ_{max} 226, 285, 293 mμ; $\nu_{max}^{CCl_4}$: 3 400 (NH), 1 705 (C=O) cm^{-1}; n.m.r. ($CDCl_3$): 2.8 (multiplet, 4H, aromatic), 6.30 (singlet, 3H, CH_3O), 9.10 τ (triplet, 3H, CH_2CH_3). This compound was subsequently shown to be coronaridine by comparison with an authentic sample.

The amorphous material was taken up in anhydrous ether and the hydrochloride salt formed by passing in dry hydrogen chloride. Two recrystallizations from acetone–ether afforded the hydrochloride as needles, m.p. 221–223° (decomp.); ν_{max}^{Nujol}: 3 160 (NH), 2 530 (NH), 1 715 cm^{-1} (C=O). An authentic sample of coronaridine hydrochloride, m.p. 221–223° (decomp.), prepared from a sample of coronaridine, completely established the identity (mixed melting point, t.l.c., and infrared spectra).

Benzene–ether (1:1) eluted a compound (440 mg) which was recrystallized from petroleum ether (b.p., 60–80°) to afford prisms, m.p. 143–145.5°; $[\alpha]_D^{23}$ +49° ($CHCl_3$); λ_{max} 225, 286, 293 mμ; ν_{max}^{KBr}: 3 350 (NH), 1 700 cm^{-1} (C=O); n.m.r. ($CDCl_3$): 2.8 (multiplet, 4H, aromatic), 6.38 (singlet, 3H, CH_3O), 9.04 τ (triplet, 3H, CH_2CH_3). This material was identified as dihydrocatharanthine by comparison with an authentic sample which we prepared by hydrogenation of catharanthine.

Reaction of Cleavamine with Concentrated Hydrochloric Acid

A mixture of cleavamine (100 mg), stannous chloride (180 mg), and mossy tin (30 mg) in concentrated hydrochloric acid (3 ml) was heated under reflux in a nitrogen atmosphere for 75 min. The reaction mixture was then treated with dilute aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* provided 80 mg of a crude reaction product. This product was shown by thin-layer chromatography to consist mainly of cleavamine and a small amount of a very polar component, but *no* dihydrocleavamine. It should be emphasized that t.l.c. can readily detect even very minute amounts of any dihydrocleavamine, and so its absence is conclusively established.

ACKNOWLEDGMENTS

Financial aid from the National Cancer Institute of Canada, the National Research Council of Canada, and Eli Lilly and Company is very gratefully acknowledged. We express our sincere thanks to Drs. M. Gorman and N. Neuss, Eli Lilly and Company, for the generous samples of catharanthine hydrochloride, descarbomethoxycatharanthine, coronaridine, and 4α-dihydrocleavamine, and for their results on the chemistry of catharanthine before publication. We also express our gratitude to Professor Carl Djerassi for the mass spectrometric measurements. One of us (R. T. B.) is indebted to the Canadian Commonwealth Scholarship and Fellowship Committee for a scholarship.

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