cation by preparative tlc. Silica gel GF_{254} plates (20 × 60 cm, 0.5 mm thick) were used, with ethyl acetate–ethanol (10:7) being employed as developing solvent. Approximately 150 mg of the crude mixture was applied per plate, and the (+)-aspidospermidine band of each plate was eluted with warm methanol. Evaporation of the combined eluants produced 200 mg of crystalline material. Recrystallization from acetone afforded 180 mg (22.5%) of colorless needles, which were identified as pure (+)-aspidospermidine (X) by comparison with an authentic sample: mp 119.5–121°, lit.[23] mp 119–120°, mmp 119–120.5°; $[\alpha]^{23}D$ +21° (*c* 0.99, ethanol), lit.[23] $[\alpha]^{23}D$ +24 ± 5° (*c* 0.39, ethanol); identical R_f value on tlc (silica gel, 2:1 ethyl acetate–ethanol); identical infrared spectra (KBr disks); λ_{max} 242.5, 296 mμ (log ε 3.79, 3.44, respectively); λ_{min} 225, 270 mμ (log ε 3.55, 2.97, respectively); nmr τ 2.70–3.55 (diffuse, 4 H, aromatic), 6.25–7.25 (diffuse, 4 H), 9.39 (triplet, 3 H, CH_2CH_3).

Acknowledgment. We gratefully acknowledge financial support from the National Research Council of Canada and the National Cancer Institute of Canada. One of us (R. T. B.) is indebted to the Canadian Commonwealth Scholarship and Fellowship Committee for a scholarship during this study. We express our sincere thanks to Drs. M. Gorman and N. Nuess, Eli Lilly and Company, for generous supplies of catharanthine hydrochloride.

Total Synthesis of Indole and Dihydroindole Alkaloids. II.[1] The Partial Synthesis of Some Nine-Membered Ring Intermediates from Catharanthine

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Abstract: An investigation of the reaction of catharanthine with zinc in glacial acetic acid is presented. Four isomeric carbomethoxydihydrocleavamine derivatives have been isolated and fully characterized. It is also shown that heating catharanthine in a mixture of acetic acid and sodium borohydride provides a very convenient method for the preparation of the previously unknown 18β-carbomethoxycleavamine. These compounds provide the desired intermediates for the synthesis of various Iboga alkaloids.

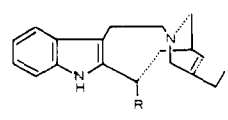
The potential interest of the cleavamine and quebrachamine ring systems in the laboratory synthesis of dihydroindole alkaloids has already been demonstrated.[1] Further investigations of this approach required the availability of various cleavamine derivatives, and, therefore, their preparation came under study in our laboratory.

Cleavamine (I) was initially obtained by the Lilly group in their investigations on Vinca alkaloids,[2,3] while a further study in our laboratory on the acid-catalyzed reactions of catharanthine allowed the isolation of two dihydrocleavamine derivatives in addition to cleavamine.[4] None of the products possessing the cleavamine skeleton still retained the ester function and were, therefore, of little interest to our immediate requirement.

The reaction of catharanthine with zinc in acetic acid on the other hand was shown to yield a carbomethoxydihydrocleavamine,[3,5] and it became of immediate importance to our investigations. It was necessary for us to study this reaction in more detail in the hope that other carbomethoxydihydrocleavamine or carbomethoxycleavamine derivatives could be isolated.

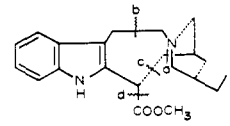
In our hands, catharanthine, on reaction with zinc dust in refluxing glacial acetic acid, provided a complex mixture from which four compounds (representing approximately 40% of the crude reaction mixture) could be isolated and characterized. The major component (isomer C),[6] mp 172°, was identical with the previously reported carbomethoxydihydrocleavamine[3,5,7] while the other three compounds required characterization.

Isomer A, mp 144–147°, appeared to be another carbomethoxydihydrocleavamine derivative when elemental analysis and mass spectrometry established the molecular formula, $C_{21}H_{28}N_2O_2$. The molecular ion (*m/e* 340) was accompanied by fragments which were immediately reminiscent of the quebrachamine and cleavamine fragmentation process[3] (Figure 1). Thus, the fragment at *m/e* 215 may arise from cleavage at a and b as shown in II, while loss of the ester group (d) from the latter would generate the species at *m/e* 156.



I, R = H

IX, R = $COOCH_3$



II

(1) Part I. J. P. Kutney, E. Piers, and R. T. Brown, *J. Amer. Chem. Soc.*, **92**, 1700 (1970).
(2) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *ibid.*, **84**, 1509 (1962).
(3) M. Gorman, N. Neuss, and N. J. Cone, *ibid.*, **87**, 93 (1965).
(4) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, **43**, 1545 (1965).
(5) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Buchi, and R. E. Manning, *J. Amer. Chem. Soc.*, **86**, 1440 (1964).
(6) For the sake of clarity, the compounds are designated A, B, C, D in order of increasing polarity on a silica gel chromatoplate.
(7) We are very grateful to Dr. M. Gorman, Lilly Research Laboratories, for an authentic sample of this compound.

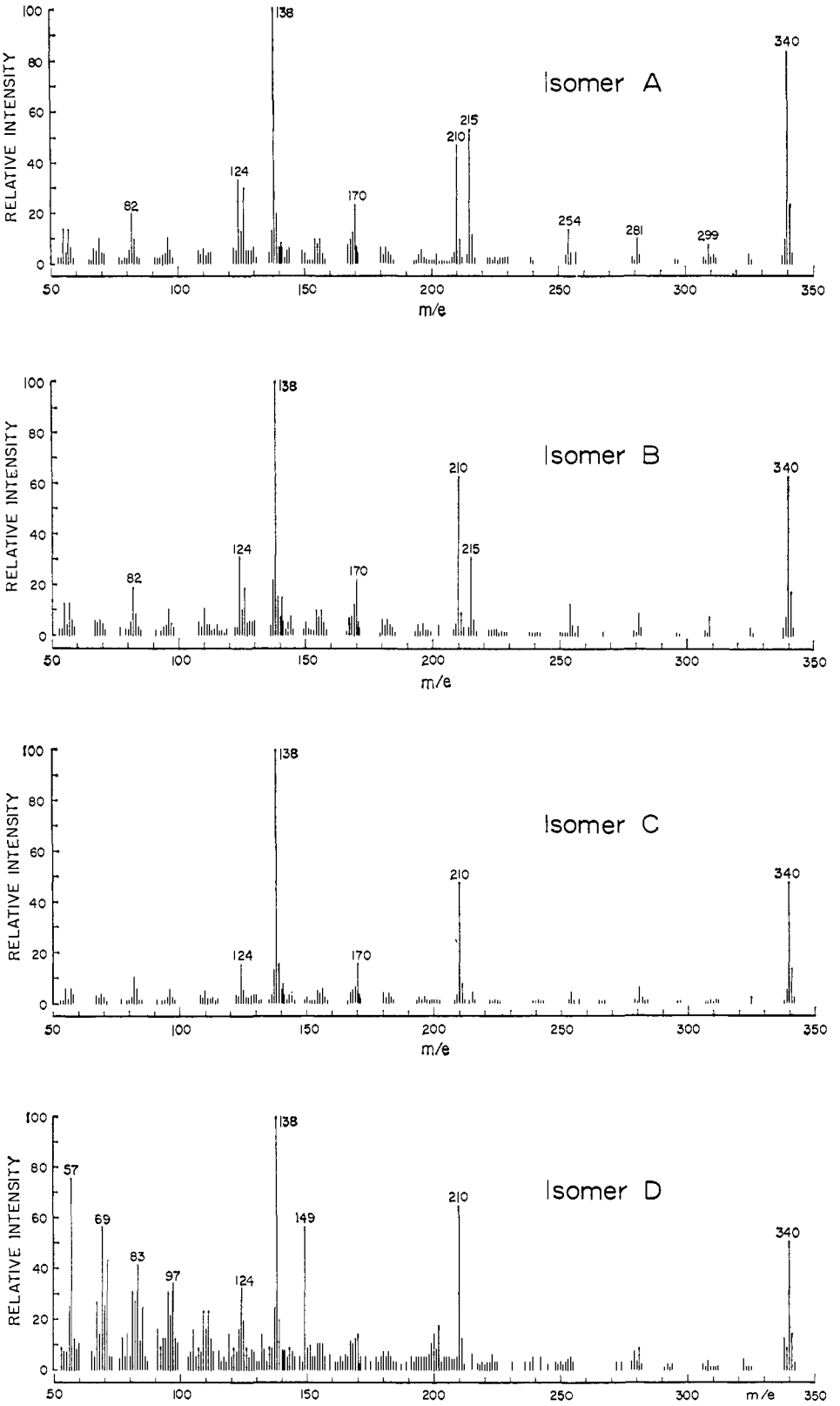


Figure 1. Mass spectra of the four isomeric carbomethoxydihydrocleavamines.

The accompanying piperidine fragment arising from this cleavage would be seen at *m/e* 124. Alternative fission at b, c, and d would give rise to the fragments at *m/e* 144, 143, and 138. Conclusive evidence for the structure of this compound was obtained when the known carbomethoxydihydrocleavamine (isomer C), on treatment with boron trifluoride, was converted to isomer A. This experiment clearly established that these compounds were merely isomeric at C_{18}.

Isomer B, mp 146–149°, was also a carbomethoxydihydrocleavamine derivative (Figure 1), since acidic hydrolysis and decarboxylation gave 4β-dihydrocleavamine. For comparison, isomer C, under these conditions, gave rise to a dihydrocleavamine (now designated

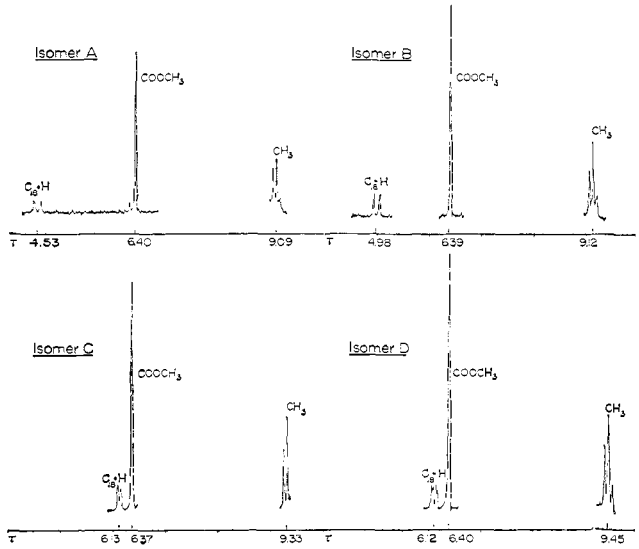


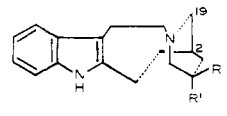
Figure 2. Pertinent regions of nmr spectra of the four carbomethoxydihydrocleavamine isomers.

as 4α) identical with that previously obtained by the Lilly workers[8] and *not* identical with the 4β isomer obtained from B.

Isomer D, mp 226–229°, was the fourth compound isolated from the zinc–acetic acid reaction. Evidence for a carbomethoxydihydrocleavamine formulation was obtained as above. Reaction of D with boron trifluoride provided B, and consequently, the relationship between these isomers was apparent.

The above results established the gross structures of the four compounds obtained, but clearly, insufficient evidence has been presented to differentiate between them. We would now like to discuss the data which allow complete structural and stereochemical assignments to isomers A, B, C, and D.

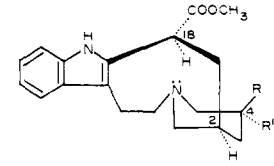
X-Ray evidence on cleavamine methiodide[8,9] established the absolute configuration at C_2 in this molecule. On this basis, the stereochemistry at C_2 in the dihydrocleavamine, obtained by catalytic reduction of cleavamine,[3] is also defined. Furthermore, we have also shown by the X-ray method[10] that the cyclization product derived from this compound is 7β-ethyl-5-desethylaspidospermidine. It is, therefore, established that this dihydrocleavamine isomer can now be termed as 4β-dihydrocleavamine (III).[11,12] An extension of this argument allows the assignment, 4α-dihydrocleavamine (IV), to the isomer obtained by removal of the ester function in isomer C. In consideration of the experiments mentioned earlier, it is clear that isomers A and C



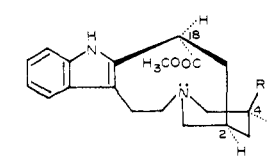
III, R' = CH_2CH_3; R = H
IV, R = H; R = CH_2CH_3

now belong to the 4α-dihydrocleavamine series and differ only in stereochemistry at C_{18}. Similarly, isomers B and D are in the 4β series and merely differ at C_{18}.

The remaining question of stereochemistry at C_{18} in the two series was settled by nmr spectroscopy. Figure 2 illustrates the pertinent regions for $C_{18}H$, the ester and ethyl groups in isomers A–D. Isomers A and B possess multiplets in the region τ 4.5–5.0 for $C_{18}H$, whereas the corresponding proton absorbs at higher field in compounds C and D (τ 6.0–6.2). This rather dramatic difference in the resonance frequency is readily explicable in terms of the appropriate conformational structures which are possible in these two series (V–VIII). In V and VI, the proton at C_{18} is in close proximity to the basic nitrogen atom of the piperi-



V, R = H; R' = CH_2CH_3
VI, R = CH_2CH_3; R' = H



VII, R = H; R' = CH_2CH_3
VIII, R = CH_2CH_3; R' = H

dine moiety, and it would be expected to absorb at a lower frequency. Such a situation does not prevail in VII and VIII, and a more normal resonance frequency for $C_{18}H$ would be anticipated. On this basis, and in conjunction with the previous arguments presented above, isomer A is now completely defined as 18β-carbomethoxy-4α-dihydrocleavamine (V), while B is the 18β isomer in the 4β series (VI). Isomer C, the major component obtained previously in another laboratory,[5] is the 18α-carbomethoxy compound in the 4α series (VII), while D can now be assigned structure VIII.

It is appropriate to mention here that similar nmr arguments have been employed by Mokry and Kompis in establishing the stereochemistry of the structurally related Vinca alkaloids, vincaminorine and vincaminoreine.[13]

Our further interest in finding a route to the unknown carbomethoxycleavamine (IX) series led us to consider hydride reduction of the intermediates derived from the acid-catalyzed ring opening of catharanthine.[3,4] When catharanthine was treated with sodium borohydride (in acid medium), a crystalline compound, $C_{21}H_{26}N_2O_2$, mp 121–123° (63% yield), was obtained. The nmr spectrum was immediately indicative of an 18β-carbomethoxycleavamine system. Acid hydrolysis and decarboxylation of this crystalline compound yielded cleavamine. The structure of this product was thus established to be the desired derivative (IX).

These investigations provided the necessary nine-membered ring intermediates for the synthesis of Iboga alkaloids, exemplified by coronaridine as well as the unsaturated system known in catharanthine. Experiments in this direction are reported in the following publications.

Experimental Section[14]

Zinc–Acetic Acid Reduction of Catharanthine. A mixture of catharanthine (4.9 g) and zinc dust (34 g) in glacial acetic acid (125

(8) J. P. Kutney, J. Trotter, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind.* (London), 648 (1963).
(9) N. Camerman, and J. Trotter, *Acta Crystallogr.*, 17, 384 (1964).
(10) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Lett.*, 637 (1965).
(11) It must be noted that C_7 in the conventional Aspidosperma numbering system is C_4 in the Iboga system.
(12) For the sake of convenience, we designate the β orientation to the C_4 ethyl group which is *trans* to the hydrogen atom at C_2 as indicated in the structure III and VI in this publication.
(13) J. Mokry and I. Kompis, *Lloydia*, 27, 428 (1964).
(14) For general information, see ref 1.

ml) was heated under reflux, with vigorous stirring, in a nitrogen atmosphere for 4 hr. The hot mixture was filtered and the filtrate was evaporated under reduced pressure until most of the acetic acid was removed. The residue was made basic by addition of dilute aqueous ammonia, and the resulting mixture was extracted thoroughly with ether. The combined extracts were washed with saturated brine and dried over anhydrous sodium sulfate. Removal of the ether afforded a gummy residue which was subjected to chromatography on alumina (150 g). Elution with petroleum ether (bp 30–60°) (1200 ml) afforded 1.13 g of crystalline 18α-carbomethoxy-4α-dihydrocleavamine (VII) (isomer C). Recrystallization from methanol gave colorless blocks, mp 169–171°, $[\alpha]^{23}D$ +100° ($CHCl_3$); λ_{max} 227, 286, 293 mμ (log ε 4.50, 3.89, 3.86, respectively); ν_{max}^{KBr} 3375 (NH), 2755 (Bohlmann band), 1709 ($COOCH_3$) cm^{-1}; nmr (100 MHz) τ 1.00 (singlet, 1 H, NH), 2.76 (diffuse, 4 H, aromatic), 6.13 (doublet, 1 H, C-18 proton), 6.37 (singlet, 3 H, $COOCH_3$), and 9.33 (triplet, 3 H, CH_2CH_3). This compound was found to be identical (mp and mmp 169–171°, infrared, nmr, and tlc R_f value) with the carbomethoxydihydrocleavamine reported previously.[3,5,7]

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; O, 9.40; mol wt 340.215. Found: C, 73.95; H, 8.10; N, 8.31; O, 9.56; mol wt 340.214 (high-resolution mass spectrometry).

Further elution in the above chromatography with petroleum ether (bp 30–60°) provided a mixture (1.14 g) of the three remaining isomeric carbomethoxydihydrocleavamines which were separated by preparative tlc. Silica gel GF_{254} plates (30 × 60 cm, 9.5 mm thickness) were used, with 150 mg of the mixture being applied to each plate. After development with 3:1 chloroform–ethyl acetate, each desired band was scraped off the plate and eluted with warm methanol. Evaporation of the eluants gave the desired crystalline carbomethoxydihydrocleavamines.

18β-Carbomethoxy-4α-dihydrocleavamine (V, 0.28 g) (isomer A) was recrystallized from methanol, affording prisms, mp 144–147°, $[\alpha]^{23}D$ +18° ($CHCl_3$); λ_{max} 227, 286, 294 mμ (log ε 4.54, 4.02, 3.97, respectively); ν_{max}^{KBr} 3340 (NH), 2760 (Bohlmann band), 1707 ($COOCH_3$) cm^{-1}; nmr (100 MHz) τ 1.40 (singlet, 1 H, NH), 2.81 (diffuse, 4 H, aromatic), 4.53 (doublet, 1 H, C-18 proton), 6.40 (singlet, 3 H, $COOCH_3$), and 9.09 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; O, 9.40; mol wt 340.215. Found: C, 74.10; H, 8.06; N, 8.15; O, 9.61; mol wt 340.215 (high-resolution mass spectrometry).

18β-Carbomethoxy-4β-dihydrocleavamine (VI, 0.25 g) (isomer B) was obtained as prisms from methanol, mp 146–149°, $[\alpha]^{23}D$ −66° ($CHCl_3$); λ_{max} 227, 286, 294 mμ (log ε 4.54, 4.02, 3.98, respectively); ν_{max}^{KBr} 3300 (NH), 2755 (Bohlmann band), 1695 ($COOCH_3$) cm^{-1}; nmr (100 MHz) τ 1.37 (singlet, 1 H, NH), 2.83 (diffuse, 4 H, aromatic), 4.98 (doublet, 1 H, C-18 proton), 6.39 (singlet, 3 H, $COOCH_3$), and 9.12 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; O, 9 40; mol wt 340.215. Found: C, 73.87; H, 8.20; N, 8.33; O, 9.54; mol wt 340.215 (high-resolution mass spectrometry).

18α-Carbomethoxy-4β-dihydrocleavamine (VIII, 0.22 g) (isomer D) was recrystallized from acetone, giving small blocks, mp 226–229°; λ_{max} 226, 286, 294 mμ (log ε 4.50, 3.92, 3.90, respectively); ν_{max}^{KBr} 3335 (NH), 2760 (Bohlmann band), 1720 ($COOCH_3$) cm^{-1}; nmr (100 MHz) τ 1.30 (singlet, 1 H, NH), 2.84 (diffuse, 4 H, aromatic), 6.12 (pair of doublets, 1 H, C-18 proton), 6.40 (singlet, 3 H, $COOCH_3$), and 9.45 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{28}O_2N_2$: C, 74.08; H, 8.29; N, 8.23; O, 9.40; mol wt 340.215. Found: C, 74.18; H, 8.25; N, 8.21; O, 9.45; mol wt 340.215 (high-resolution mass spectrometry).

Epimerization of 18α-Carbomethoxy-4α-dihydrocleavamine (VII) (Isomer C). To a solution of compound VII (500 mg) in dry benzene (10 ml) was added boron trifluoride etherate (1 ml) and the resulting solution was refluxed under an atmosphere of nitrogen for 6 hr. After cooling, the solution was poured into saturated aqueous sodium bicarbonate and the resulting mixture was extracted thoroughly with dichloromethane. The combined extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residual material was purified by preparative tlc (silica gel, chloroform), affording 200 mg of starting material (VII), as shown by mp (169–171°), mmp (169–171°), infrared and tlc, and 175 mg of 18β-carbomethoxy-4α-dihydrocleavamine (V) (isomer A). The latter was identical (mp 144–147° and mmp 144–147°, infrared, tlc) with compound V prepared previously (see above).

Epimerization of 18α-Carbomethoxy-4β-dihydrocleavamine (VIII) (Isomer D). Compound VIII (22 mg) was treated with boron trifluoride etherate in benzene solution under conditions identical with those described above for compound VII. Purification of the crude product by preparative tlc (silica gel, 3:1 chloroform–ethyl acetate) afforded 7 mg of starting material (VIII), as shown by mp (226–229°), infrared and tlc, and 8 mg of 18β-carbomethoxy-4β-dihydrocleavamine (VI) (isomer B). The latter was identical (mp 146–149° and mmp 146–149°, infrared, tlc) with an authentic sample obtained previously (see above).

Decarbomethoxylation of 18β-Carbomethoxy-4α-dihydrocleavamine (V) (Isomer A). A solution of compound V (33 mg) in 5 *N* hydrochloric acid (1 ml) was heated, under an atmosphere of nitrogen, at 95° for 8 hr. The solution was cooled in ice and made basic by addition of dilute aqueous ammonia. The resulting mixture was extracted with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal of solvent afforded amorphous material which was identical, as shown by infrared and tlc (silica gel, ethyl acetate), with an authentic sample of 4α-dihydrocleavamine (IV).[4]

Decarbomethoxylation of 18β-Carbomethoxy-4β-dihydrocleavamine (VI) (Isomer B). Compound VI (30 mg) was decarbomethoxylated under conditions identical with those described above. The product, which was crystallized from methanol, gave mp 136–138°, and was found to be identical, as shown by mp and mmp (136–138°), infrared, and tlc (silica gel, 1:1 chloroform–ethyl acetate), with 4β-dihydrocleavamine (III).[4]

Decarbomethoxylation of 18α-Carbomethoxy-4α-dihydrocleavamine (VII) (Isomer C). Decarbomethoxylation of compound VII (500 mg) under conditions identical with those described above, gave 4α-dihydrocleavamine (IV), identical (infrared and tlc) with an authentic sample.[4]

18β-Carbomethoxycleavamine. A solution of catharanthine hydrochloride (5.5 g) in glacial acetic acid (250 ml) was heated to 90° in a 1-l. three-necked flask equipped with a mechanical stirrer and a reflux condenser. Sodium borohydride (17.5 g) was added at intervals to keep the solution gently refluxing. After 1 hr, the reaction mixture was cooled to 10°, poured into aqueous ammonia, and the resulting mixture was extracted thoroughly with dichloromethane. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residual light brown oil was dissolved in hot methanol (7 ml) and the product was allowed to crystallize, giving 1.9 g of pure 18β-carbomethoxycleavamine (IX), mp 121–123°. The mother liquor was evaporated and the residual oil was subjected to column chromatography on Woelm silica gel, activity I (75 g). Elution with chloroform produced a further gram of crystalline 18β-carbomethoxycleavamine (IX), mp 121–123°; yield 2.9 g (63%); λ_{max} 225, 227(sh), 287, 294 mμ (log ε 4.55, 3.89, 3.95, 3.92, respectively); λ_{min} 255, 292 mμ (log ε 3.51, 3.88, respectively); $\nu_{max}^{CHCl_3}$ 3415 (NH), 1708 ($COOCH_3$) cm^{-1}; nmr (100 MHz) τ 1.45 (singlet, 1 H, NH), 2.47–3.10 (diffuse, 4 H, aromatic), 4.76 (multiplet, 1 H, olefinic H), 4.89 (doublet, 1 H, C-18 proton), 6.42 (singlet, 3 H, $COOCH_3$), 7.97 (quartet, 2 H, CH_2CH_3), and 8.96 (triplet, 3 H, CH_2CH_3).

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.35; H, 7.80; N, 8.50.

Decarbomethoxylation of 18β-Carbomethoxycleavamine (IX). A solution of compound IX (50 mg) in 5 *N* hydrochloric acid (2 ml) was heated at 90° for 3 hr. The solution was cooled, poured into aqueous ammonia, and the resulting alkaline mixture was extracted thoroughly with dichloromethane. The combined extracts were washed with water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure to provide, after recrystallization from methanol, 30 mg of a crystalline material. The latter was shown by mp (117–119°), mmp (117–119°), and infrared spectra to be identical with an authentic sample of cleavamine (I).[4]

Hydrogenation of 18β-Carbomethoxycleavamine (IX). A small sample of compound IX was hydrogenated (room temperature and atmospheric pressure) in ethyl acetate over Adam's catalyst. Filtration, followed by evaporation of the filtrate under reduced pressure, afforded 18β-carbomethoxy-4β-dihydrocleavamine (VI), identified by comparison (mp 146–149° and mmp 146–149°, infrared) with an authentic sample (see above).

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