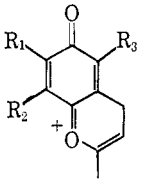
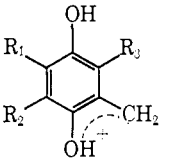
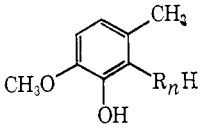
spectrometric analysis. Specifically, peaks with appropriate relative intensities were observed at *m/e* 818 (M), 803 (M − 15), 191 (Xc), and 153 (XIc). Although isolation of a pure sample of this compound has not yet been achieved, these data support its presence. The possibility that the conversion V → VII could occur *via* 2-decaprenyl-6-methoxy-3-methylphenol (VIa) led to a search for this phenol derivative which has not yet been successful, but is continuing.



Xa, *m/e* 235, $R_1=R_2=OCH_3$; $R_3=CH_3$
b, *m/e* 205, $R_1=H$; $R_2=OCH_3$; $R_3=CH_3$
c, *m/e* 191, $R_1=R_3=H$; $R_2=OCH_3$



XIa, *m/e* 197
b, *m/e* 167
c, *m/e* 153



VIa

Acknowledgment. We are grateful to Dr. Raffaele F. Muraca and Mrs. Julia S. Whittick for the mass spectra which have significantly aided structural elucidation. This research was partially supported by the Merck Sharp and Dohme Research Laboratories, Rahway, N. J., and we express our appreciation to Dr. Max Tishler.

(17) On leave of absence from The Royal Veterinary and Agricultural College, Copenhagen, Denmark.

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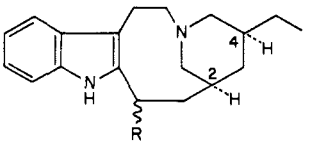
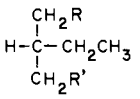
The Total Synthesis of *dl*-Dihydrocleavamine, *dl*-Carbomethoxydihydrocleavamine, *dl*-Coronaridine, and *dl*-Dihydrocatharanthine. A General Entry into the Iboga and Vinca Alkaloids

Sir:

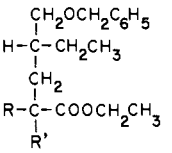
Previous communications from our laboratory[1-3] have demonstrated the utility of a transannular cyclization approach in the synthesis of Aspidosperma, Vinca, and Iboga alkaloids. The stereochemical problems associated with the total syntheses of such molecules are simplified considerably by this method, since we have shown[4,5] that stereospecificity can be achieved and, therefore, the crucial nine-membered ring intermediates are amenable to laboratory synthesis without serious consideration of stereochemistry at the various stages of the synthetic pathway. Very recently[6] we described a new total synthesis of *dl*-quebrachamine, the essential intermediate for the Aspidosperma series, and now we report our work on the total synthesis of dihydrocleavamine (I; R = H) and its ester derivative (I; R = $COOCH_3$) which are the necessary intermediates for the Iboga and Vinca series.



I



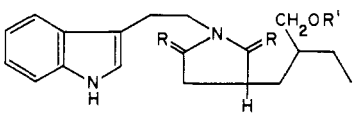
II



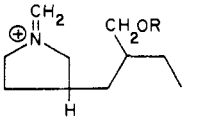
III

The monosodium salt of 2-ethyl-1,3-propanediol (II; R = R′ = OH) on reaction with benzyl chloride in xylene provided the benzyl ether II (R = OH, R′ = $OCH_2C_6H_5$)[7] in 77% yield, bp 130–133° (2 mm), which was converted to the chloride II (R = Cl, R′ = $OCH_2C_6H_5$, 66% yield), bp 88–90° (0.3 mm), in a conventional manner (thionyl chloride in dimethylaniline). The latter substance was alkylated onto the sodio derivative of diethyl malonate to obtain the diester III (R = H, R′ = $COOCH_2CH_3$, 70% yield), bp 155–160° (0.3 mm). This compound was alkylated (sodium in ether) with ethyl bromoacetate to yield the triester III (R = $CH_2COOCH_2CH_3$, R′ = $COOCH_2CH_3$, 78% yield), bp 195–200° (0.2 mm), which in turn was hydrolyzed (alkali), thermally decarboxylated (170°) to a diacid, and finally esterified (ethanol–sulfuric acid) to provide the desired succinate ester derivative III (R = $CH_2COOCH_2CH_3$, R′ = H, 78% yield).[8]

Condensation of the succinate with tryptamine provided, in 77% yield, the succinimide IV (R = O, R′ = $CH_2C_6H_5$), $C_{26}H_{30}N_2O_3$, which exhibited the following spectral properties: λ_{max}^{EtOH} 222, 274 (sh), 283, and 291 mμ; ν_{film} 5.68 and 5.90 μ; nmr signals:[9] τ 3.0 (doublet, α proton on indole), 5.5 (singlet, C_6H_5-CH_2O), 6.25 (triplet, CH_2N), 6.65 (broad doublet, $OCH_2CH<$), 6.8–8.0 (5 H, CH_2CH_2N, CH_2CO, and $>CHCO$), and 9.15 (triplet, CH_3). Lithium aluminum hydride reduction of the latter provided the amine IV (R = H_2, R′ = $CH_2C_6H_5$, 90% yield), which still retained the normal indole absorption in the ultraviolet



IV



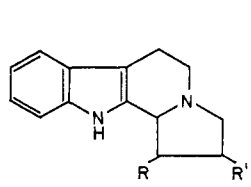
V

(1) J. P. Kutney and E. Piers, *J. Am. Chem. Soc.*, **86**, 953 (1964).
(2) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2286 (1964).
(3) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2287 (1964).
(4) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Letters*, 637 (1965).
(5) J. P. Kutney, R. T. Brown, and E. Piers, *Can. J. Chem.*, 44, 637 (1966).
(6) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966).
(7) Satisfactory elemental analyses were obtained for all new compounds reported. In addition, high-resolution mass spectrometry, using an AEI MS9 mass spectrometer, was employed in most instances to establish the molecular formulas.
(8) It must be emphasized again that no separation of the individual stereoisomers is necessary at this point or at subsequent steps in the synthesis, since the stereochemistry of only *one* center, namely C_2, in dihydrocleavamine determines the total stereochemistry of the final cyclization product. Since the absolute configuration of 4β-dihydrocleavamine is already established at *both* asymmetric centers,[5] the stereochemistry of the succinate ester and all subsequent synthetic intermediates follows directly. For this reason, no discussion of this problem is presented here, but the problem will be treated in a subsequent detailed paper.
(9) All nmr spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard with a Varian A-60 spectrometer. All signals are reported in τ units.

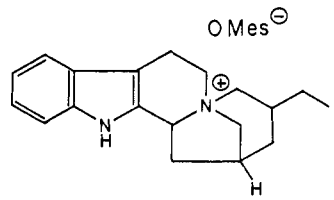
but had lost the characteristic imide absorption in the infrared spectrum. The molecular formula $C_{26}H_{34}N_3O$ was established by high-resolution mass spectrometry which provided the value 390.267 (calcd: 390.267). As already noted previously,[6] this type of molecule fragments rapidly under electron impact to provide a very significant peak at *m/e* 260 due to the ion V (R = $CH_2C_6H_5$).

The amine was treated with excess mercuric acetate (methanol–acetic acid) and the crude product was reduced immediately with sodium borohydride[6] to provide a mixture of six compounds in 42% yield. One of the major components was the desired cyclic amine VI (R = H, R′ = $CH_2CH(Et)CH_2OCH_2C_6H_5$), $C_{26}H_{32}N_2O$ (found: 388.251; calcd: 288.251), no nmr α proton signal on the indole ring and a typical indole chromophore in the ultraviolet spectrum.[10] The mass spectrum of this compound was completely different from that of the amine IV, and with peaks at *m/e* 184, 170, 156, etc., was immediately reminiscent of the analogous compound in the quebrachamine series.[6]

Catalytic debenzylation (palladium on charcoal) converted the benzyloxyamine to the amino alcohol VI (R = H, R′ = $CH_2CH(C_2H_5)CH_2OH$, 85% yield), $C_{19}H_{26}N_2O$ (found: 298.204; calcd: 298.205). Apart from the normal indole ultraviolet spectrum, the nmr spectrum showed a complete absence of the characteristic benzyl ether proton signals mentioned above.



VI



VII

The total synthesis of a *dl*-dihydrocleavamine was completed when the quaternary mesylate, VII, formed directly from the reaction of the amino alcohol with methanesulfonyl chloride in pyridine, was reduced with sodium and liquid ammonia.[6] The reaction product was identical with an authentic sample of 4β-dihydrocleavamine (I; R = H) obtained previously by catalytic reduction of cleavamine. The isomeric 4α-dihydrocleavamine (α-ethyl group at C_4 in I) is also obtained and shown to be identical with an authentic sample prepared from the acid hydrolysis of carbomethoxydihydrocleavamine (infrared, thin-layer chromatography, mass spectrometry in both instances).

Introduction of the ester group to complete the total synthesis of carbomethoxydihydrocleavamine was achieved as follows. Conversion of 4β-dihydrocleavamine to a chloroindolenine was accomplished by means of *t*-butyl hypochlorite.[11] The mass spectrum of the latter compound, $C_{19}H_{25}N_2Cl$, with its molecular ion peak at *m/e* 316 (as well as 318 for ^{37}Cl), its base peak at *m/e* 281 (M − Cl), and peaks normally encountered in the fragmentation of the cleavamine system[12] allowed a normal formulation for this compound.[11] Regeneration of 4β-dihydrocleavamine from lithium aluminum hydride reduction of the chloroindolenine[11] provided further confirmation for its structure.

Reaction of the chloroindolenine with potassium cyanide[11] gave a cyanodihydrocleavamine (I; R = CN), $C_{20}H_{25}N_3$ (found: 307.205; calcd: 307.205), normal indole absorption; ν_{film} 4.5 μ (C≡N); multiplet centered at τ 5.95 in the nmr (HC–CN); typical dihydrocleavamine fragmentation in the mass spectrum.[12] The latter compound on treatment with methanolic hydrochloric acid provided carbomethoxy-4β-dihydrocleavamine (I; R = $COOCH_3$) identical in every respect with an authentic sample of I prepared in our laboratory from the reaction of catharanthine with acetic acid in the presence of zinc dust.[13]

This work now completes the total synthesis of *dl*-coronaridine and *dl*-dihydrocatharanthine in view of our previously reported cyclization.[3] Since the conversion of coronaridine to ibogamine has also been accomplished,[14] our work extends to this series as well.

It is now evident that the transannular cyclization approach is the most general method yet developed for the total synthesis of Aspidosperma, Vinca, and Iboga alkaloids.

Very recently[15] a total synthesis of the Iboga alkaloids has also been achieved by a completely different route.

Acknowledgment. Financial aid from the National Cancer Institute of Canada and the National Research Council of Canada is gratefully acknowledged.

(10) The alternative cyclization product VI (R = $CH_2CH(Et)CH_2OCH_2C_6H_5$; R′ = H) does not lead to a dihydrocleavamine. A further discussion of this reaction will be presented in the detailed paper.

(11) G. Buchi and R. E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966).

(12) M. Gorman, N. Neuss, and N. J. Cone, *ibid.*, **87**, 93 (1965).

(13) Unpublished results from our laboratory. See also ref 12.

(14) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Am. Chem. Soc.*, **82**, 1142 (1960).

(15) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **87**, 2073 (1965); **88**, 3099 (1966).

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Received August 15, 1966

The Reaction of Trialkylboranes with Dimethyloxosulfonium Methylide

Sir:

The migration of a group from boron to adjacent oxygen and nitrogen is a well-known occurrence which provides the basis for the synthetically important oxidation of organoboranes to alcohols[1-3] as well as their conversion to amines.[4] Organoboranes are known to react with carbon monoxide,[5] isonitriles,[6] diazomethane,[7] and phenyl(bromodichloromethyl)mercury[8] by processes which appear to involve the rearrangement of a group from boron to carbon.

A consideration of these reactions makes it seem

(1) H. G. Kuivila and R. A. Wiles, *J. Am. Chem. Soc.*, **79**, 5659 (1957), and references cited therein.

(2) W. J. Wechter, *Chem. Ind.* (London), 294 (1959).

(3) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).

(4) H. C. Brown, W. R. Heydkamp, E. Brewer, and W. Murphy, *ibid.*, **86**, 3565 (1964).

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(6) (a) G. Hesse and H. Witte, *Angew. Chem.*, **75**, 791 (1963); *Ann.*, **687**, 1 (1965); (b) J. Casanova, Jr., and R. E. Schuster, *Tetrahedron Letters*, 405 (1964); (c) J. Casanova, Jr., H. Kiefer, D. Kuwada, and A. Boulton, *ibid.*, 703 (1965).

(7) C. E. H. Bawn and A. Ledwith, *Progr. Boron Chem.*, **1**, 345 (1964), and references cited therein.

(8) D. Seyferth and B. Prokai, *J. Am. Chem. Soc.*, **88**, 1834 (1966).