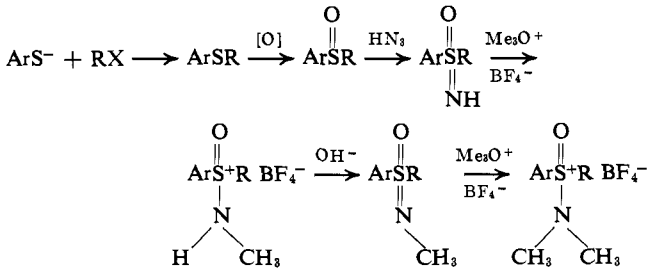
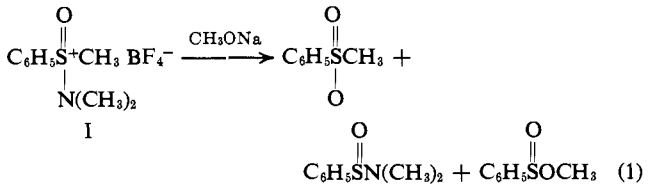
Scheme I



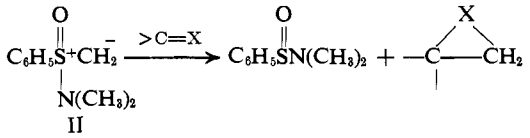
and the N-alkylsulfoximines are new classes of compounds.[5]

The reaction of N,N-dimethylaminomethylphenyloxosulfonium fluoroborate (I), mp 118–119°, δ (CH_2Cl_2) 3.1 (singlet, $N(CH_3)_2$), 3.95 (singlet, SCH_3), 7.5–8.2 (C_6H_5), with sodium methoxide in refluxing methanol is illustrated in eq 1. Presumably the methyl phenyl



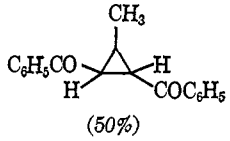
sulfone is formed in a reaction involving direct attack of the methoxide on the sulfonium sulfur, the sulfinamide by attack on the S-methyl or by decomposition of the methylide, and the ester from the initially formed amide.

Treatment of I at room temperature with sodium hydride in dimethyl sulfoxide resulted in the rapid and quantitative evolution of hydrogen with the formation of a slightly yellow solution of ylide II. Addition of

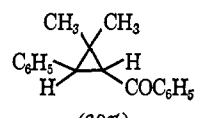


water to a solution of the ylide in dimethyl sulfoxide or tetrahydrofuran results in a strongly basic solution from which the original salt (I) could be regenerated by neutralization with fluoroboric acid. Illustrative examples of the reactions of ylide II with carbonyl compounds and electrophilic olefins are shown below.[6] In most cases the highly polar sulfinamide could be removed by passing a benzene solution of the reaction products through a short column of silica gel.

A number of similar syntheses have also been achieved employing ylides derived from ethyl and isopropyl salts; *e.g.*



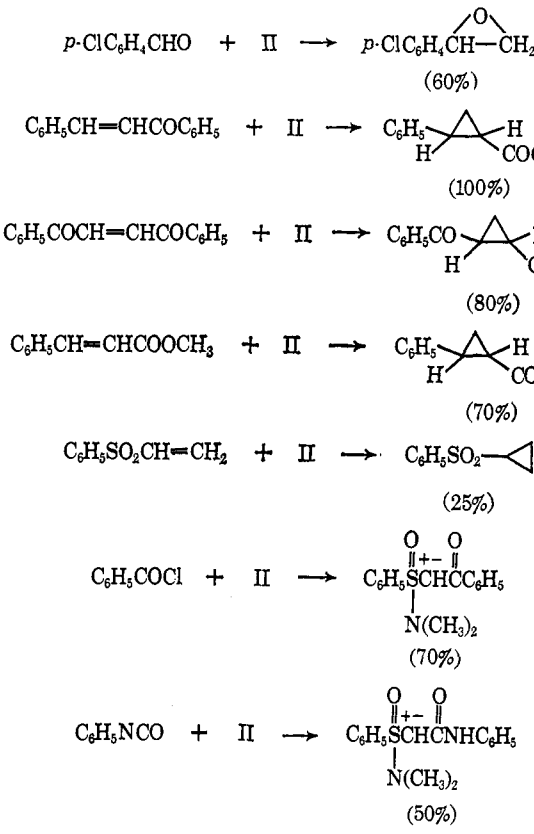
(50%)



(60%)

(5) Salts of the general structures $[R_2S(O)NH_2]^+X$ and $[R_2S(O)N{=}PR_3]^+X$ have been reported (R. Appel, H. Fehlaber, D. Hanssgen, and R. Schollhorn, *Chem. Ber.*, **99**, 3108 (1966); T. W. Rave and T. J. Logan, *J. Org. Chem.*, **32**, 1629 (1967)). In a subsequent paper we will report on the preparation of additional examples of N-alkylated sulfoximines and certain N-alkyl derivatives of sulfilimines.

(6) The reactions illustrated are similar to those previously reported for dimethyloxosulfonium methylide. For a summary of sulfur ylide chemistry see A. W. Johnson, "Ylide Chemistry," Academic Press Inc., New York, N. Y., 1966. See also H. Metzger and H. Konig, *Z. Naturforsch.*, **18b**, 987 (1963); W. E. Truce and V. V. Badiger, *J. Org. Chem.*, **29**, 3277 (1964); S. R. Landor and N. Punja, *J. Chem. Soc., C*, 2495 (1967).



(7) For additional examples of the reactions of diphenylsulfonium alkylides see A. W. Johnson, V. J. Hruby, and J. L. Williams, *J. Am. Chem. Soc.*, **86**, 9181 (1964).

(8) Alfred P. Sloan Research Fellow, 1965–1968.

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This sulfur ylide chemistry is particularly noteworthy in that extensive structural variation can be easily achieved. This has not been readily possible with other sulfur ylides, although Corey[3b,c] has recently had notable successes with the sulfonium ylides derived from diphenylsulfonium alkylides.[7] It appears that the ylides derived from our salts may be considerably more stable and may be generated under milder conditions than those employed for the simpler sulfonium ylides. An intriguing facet of this chemistry lies in the fact that optically active salts and ylides should be readily accessible. Such reagents might well yield optically active oxiranes and cyclopropanes. Extensive investigations of the chemistry of the new types of compound reported here and related compounds are under way in our laboratories.

The Total Synthesis of Some Monomeric Vinca Alkaloids: *dl*-Vincadine, *dl*-Vincaminoreine, *dl*-Vincaminorine, *dl*-Vincadifformine, *dl*-Minovine, and *dl*-Vincaminoridine[1]

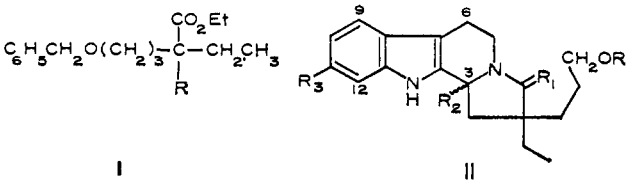
Sir:

The transannular cyclization reaction developed in these laboratories has provided a general synthetic

(1) Presented at a Symposium on the Chemistry of Natural Products, University of West Indies, Kingston, Jamaica, Jan 2–5, 1968.

entry into several families of alkaloids.[2-4] The subsequent total syntheses of the appropriate nine-membered ring intermediates, *dl*-quebrachamine and *dl*-dihydrocleavamine and its ester derivative, completed the total synthesis of several members in the Aspidosperma and Iboga series.[5,6] We now wish to report a novel sequence which completes the first total syntheses of a series of monomeric alkaloids in the Vinca family.

The key intermediate in these syntheses was the alcohol II (R = R_2 = H; R_1 = H_2; R_3 = H or OCH_3). Since one of these compounds (R_3 = H) had been obtained previously[5] in rather poor yield, its synthesis *via* a new synthetic route was first investigated.



I

II

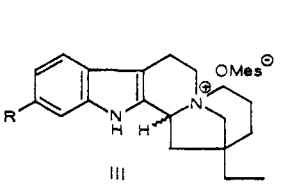
Ethyl α-(γ-benzyloxypropyl)butyrate (I, R = H) prepared previously[5] was converted to the allyl ester[7] I (R = $CH_2CH{=}CH_2$, triphenylmethyl sodium and allyl bromide, 98% yield): bp 150–153° (0.2 mm); ν_{film} 1722, 1642, 742, and 705 cm^{-1}. Reaction of this compound with osmium tetroxide–sodium periodate furnished the aldehyde I (R = CH_2CHO, 65% yield): ν_{film} 2680 and 1720 cm^{-1}; nmr signals:[8] τ 0.22 (triplet, -C*H*O).

Condensation of the aldehyde with tryptamine afforded the cyclic lactam as a mixture of two inseparable diastereoisomers (II, R = $CH_2C_6H_5$; R_1 = O; R_2 = R_3 = H; 90% yield): λ_{max}^{EtOH} 224, 273, 283, 290, 313, and 326 mμ; ν_{CHCl_3} 1670 cm^{-1}; nmr signals: 5.22 (triplet, C_3-H); no signals for α proton on the indole ring. The molecular formula, $C_{26}H_{30}N_2O_2$, was established by high-resolution mass spectrometry which provided the value 402.231 (calculated: 402.230). Lithium aluminum hydride reduction of II provided the known[5] cyclic amine II (R = $CH_2C_6H_5$; R_1 = H_2; R_2 = R_3 = H).

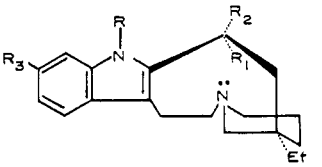
The benzyl group was removed by hydrogenolysis (10% palladium on charcoal, acetic acid) to provide in 84% yield a mixture of two isomeric alcohols (II, R = R_2 = R_3 = H; R_1 = H_2). Chromatography on alumina allowed the isolation of alcohol A which is assigned the *cis* stereochemistry (C_3-H and ethyl group are *cis*): mp 166–167°; nmr signals: τ 5.86 (triplet, C_3-H), 6.55 (triplet, CH_2OH), and 9.15 (triplet, CH_3), and *trans* alcohol B: mp 168–170°; nmr signals: τ 5.87 (triplet, C_3-H), 6.28 (broad signal, CH_2OH), and 9.30 (triplet, CH_3). The isomeric nature of these compounds was established by high-resolution mass spectrometry and from the fact that *both* alcohols afforded *dl*-quebrachamine (see below).[9]

Treatment of each of these alcohols with methanesulfonyl chloride in triethylamine provided a quantitative yield of the corresponding mesylates III (R = H). Reaction of the latter compounds with either lithium in liquid ammonia or lithium aluminum hydride in refluxing N-methylmorpholine[10] provided *dl*-quebrachamine in each instance. In this manner, *dl*-quebrachamine was obtained in 50% over-all yield from the alcohols. When this result was coupled with the above-mentioned sequence leading to the alcohols, it was clear that a vastly improved total synthesis to that previously reported[5] was available.

The mesylates III (R = H) now represented crucial intermediates in the total syntheses of the Vinca alkaloids. Reaction of these compounds with potassium cyanide in dimethylformamide afforded two isomeric cyano compounds (IV and V, R_3 = H) which were separated on silica gel chromatography. Both compounds possessed the identical molecular formula, $C_{20}H_{25}N_3$, as established by high-resolution mass spectrometry (found: 307.204; calculated: 307.204), and displayed normal indole ultraviolet spectra and nitrile absorption in the infrared (2220 cm^{-1}). One of these, IV, mp 208–210°, possessed a one-proton quartet at τ 6.08 (-C*H*CN) and a methyl triplet at τ 9.07, while the other, V, mp 164–168°, exhibited a low-field quartet at τ 3.99 (-C*H*CN) and a methyl triplet at τ 9.34 in the nmr spectra. The low-field resonance seen in the spectrum of V established that the proton α to the cyano group is in close proximity to the basic nitrogen atom and therefore deshielded.



III



IV, R = R_2 = H; R_1 = CN

V, R = R_1 = H; R_2 = CN

VI, R = R_2 = H; R_1 = $COOCH_3$

VII, R = R_1 = H; R_2 = $COOCH_3$

VIII, R = CH_3; R_2 = H; R_1 = $COOCH_3$

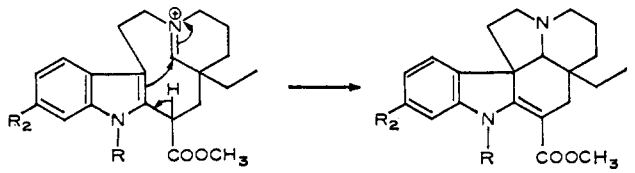
IX, R = CH_3; R_1 = H; R_2 = $COOCH_3$

Alkaline hydrolysis of these cyano compounds and esterification of the resulting acids with ethereal diazomethane provided *dl*-vincadine (VI, R_3 = H)[11-13] as a major component and *dl*-epivincadine (VII, R_3 = H) as a minor product. In both instances comparison was made with authentic samples (infrared, tlc, mass spec-

(2) J. P. Kutney and E. Piers, *J. Am Chem. Soc.*, **86**, 953 (1964).
(3) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2286 (1964).
(4) J. P. Kutney, R. T. Brown, and E. Piers, *ibid.*, **86**, 2287 (1964).
(5) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *ibid.*, **88**, 3656 (1966).
(6) J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966).
(7) Satisfactory elemental analyses were obtained for all new compounds reported. In addition, high-resolution mass spectrometry using an AEI MS9 spectrometer was employed in most instances to establish the molecular formulas.
(8) Nmr spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard with a Varian A-60 or HA100 spectrometer. All signals are reported in τ units.
(9) The stereochemical differences shown for these alcohols entail a rather involved discussion of the nmr data, and this is deferred to our detailed publication.
(10) We are very grateful to Professor L. J. Dolby, University of Oregon, for providing us with his experimental details of this method prior to publication.
(11) J. Mokry, L. Dubravkova, and P. Sefcovic, *Experientia*, **18**, 564 (1962).
(12) J. Mokry, I. Kompis, L. Dubravkova, and P. Sefcovic, *Tetrahedron Letters*, 1185 (1962).
(13) We are very grateful to Dr. I. Kompis, Institute of Chemistry, Bratislava, Czechoslovakia, for providing us with samples of vincadine, vincaminoreine, vincadifformine, and minovine.

tra). Epivincadine was synthesized from the natural alkaloid by isomerization of the ester group.

The synthesis of *dl*-vincadine also completes the total synthesis of *dl*-vincaminoreine (VIII, R_3 = H) and *dl*-vincaminorine (IX, R_3 = H) in view of the known interconversions.[14]



X, R = H
XI, R = CH_3

An entry into the pentacyclic series exemplified by vincadifformine (X, R_2 = H)[15,16] and minovine (XI, R_2 = H)[11] was now possible by means of the transannular cyclization approach.[3] Reaction of vincadine and vincaminoreine with either mercuric acetate[3] or oxygen in the presence of a catalyst (5% platinum on charcoal)[17] provided vincadifformine and minovine identical in every respect (infrared, tlc) with authentic samples.[13]

An extension of the above sequence to encompass alkaloids bearing oxygen functions, particularly methoxyl groups, in the aromatic ring was now considered. For this purpose, 6-methoxytryptamine[18] was condensed with aldehyde I to afford in 70% yield the cyclic lactam as a mixture of diastereoisomers (II, R = $CH_2C_6H_5$; R_1 = O; R_2 = H; R_3 = OCH_3): λ_{max}^{EtOH} 227, 264, 272 (sh), 297, 305 (sh), 321, and 336 mμ. Lithium aluminum hydride reduction of the latter, followed by catalytic debenzylation as described above, afforded the two isomeric alcohols. Separation of these compounds could be achieved by chromatographic techniques. The less polar alcohol II (R = R_2 = H; R_1 = H_2; R_3 = OCH_3) was obtained as a pale yellow oil which resisted crystallization; nmr signals: τ 2.74 (doublet, J_{ortho} = 8 cps, C_9-H), 3.26 (quartet, J_{ortho} = 8 cps, J_{meta} = 2.5 cps, C_{10}-H), 3.34 (doublet, J_{meta} = 2.5 cps, C_{12}-H), 6.00 (multiplet, C_3-H), 6.25 (singlet, OCH), 6.63 ($-CH_2$-OH), and 9.18 (triplet, CH_3). High-resolution mass spectrometry established the molecular formula $C_{20}H_{28}N_2O_2$ (found: 328.214; calculated: 328.215), while fragments were seen at *m/e* 214, 199, 186, etc. This compound is assigned the *cis* stereochemistry (C_3-H and ethyl group are *cis*). The *trans* alcohol[9] was obtained crystalline, mp 168–169°, and shown to be isomeric by mass spectrometry (found: 328.216).

Conversion of a mixture of these alcohols to the mesylates III (R = OCH_3) and reaction with potassium cyanide in the manner described above afforded two isomeric cyano compounds (IV and V, R_3 = OCH_3). One of these, IV, mp 186–187°, possessed an unresolved one-proton multiplet at τ 6.02 ($-CHCN$) and a methyl triplet at 9.07, while the other isomer, V, mp 191–192°, indicated a one-proton quartet at τ 4.02 ($-CHCN$) and a methyl triplet at 9.34 in the nmr spectra.

(14) J. Mokry and I. Kompis, *Lloydia*, 27, 428 (1964).
(15) J. Mokry, I. Kompis, L. Dubravkova, and P. Sefcovic, *Experientia*, 19, 311 (1963).
(16) M. Plat, J. Le Men, M. M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. France*, 2237 (1963).
(17) D. Schumann and H. Schmid, *Helv. Chim. Acta*, 46, 1996 (1963).
(18) R. B. Woodward, F. E. Boder, H. Bickel, A. J. Frey, and R. W. Kierstad, *Tetrahedron*, 2, 1 (1958).

Alkaline hydrolysis of the cyano compounds followed by esterification of the resulting acids provided 16-methoxyvincadine (VI, R_3 = OCH_3) and 16-methoxyepivincadine (VII, R_3 = OCH_3). Methylation of these esters *via* the previously published procedure[14] provided the N-methyl derivatives VIII and IX (R_3 = OCH_3). These latter substances bear the skeletal features of a natural system, since vincaminoridine, an alkaloid isolated from *Vinca minor* L., has been assigned this structure.[14] Unfortunately, no stereochemical assignment is available in this publication, and a sample of the natural alkaloid could not be obtained for comparison.

Finally, the transannular cyclization reaction mentioned above provides an obvious synthesis of XI (R_2 = OCH_3) from the esters VIII and/or IX (R_3 = OCH_3). Although this pentacyclic structure has not as yet been isolated from a natural source, it is a valuable intermediate for the total synthesis of the monomeric alkaloid vindoline and thereby provides entry into the dimeric series as well. Results in this direction will be presented in future communications.

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

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Received March 18, 1968

Photochemical Rearrangement of 1,1,4-Triphenyl-2,3-benzoxazine. Formation of an Oxazirinodihydroisoindole

Sir:

Several conjugated cyclohexadienes and hexatrienes have been shown to undergo light-induced rearrangements to bicyclo[3.1.0]hexenes.[1] No structurally related heterocyclic diene has yet been shown to undergo an analogous rearrangement. This communication describes the first example of a facile photoisomerization of a 2,3-benzoxazine, **1**, to a fused oxazirane, **2**.

Irradiation of 1,1,4-triphenyl-2,3-benzoxazine[2] (**1**) [$\lambda_{max}^{CH_3CN}$ 288 (ε 4000), 230 mμ (20,000)] in benzene or acetonitrile solution with Pyrex-filtered light produced photoisomer **2** [mp 155–156°; λ^{CH_3CN} 290 (ε 115), 230 mμ (7800)] in nearly quantitative yield. The isomeric nature of **1** and **2** was established by mass spectral and combustion data.[3] Assignment of structure **2** to the photoisomer was based on spectral and chemical evidence, outlined below.

In agreement with structure **2**, the photoproduct showed only benzenoid absorption in the ultraviolet.

(1) For leading references see (a) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, 9, 539 (1964); (b) J. Meinwald and P. H. Mazzocchi, *J. Am. Chem. Soc.*, 88, 2850 (1966); (c) W. G. Dauben and J. H. Smith, *J. Org. Chem.*, 32, 3244 (1967); (d) M. Pomerantz, *J. Am. Chem.Soc.*, 89, 694 (1967); J. Meinwald and P. H. Mazzocchi, *ibid.*, 89, 696 (1967); (e) K. R. Huffman and E. F. Ullman, *ibid.*, 89, 5629 (1967), and references therein.
(2) A. Mustafa, W. Askar, M. Kamel, A. F. A. Shalaby, and A. E. A. E. Hassen, *ibid.*, 77, 1612 (1955).
(3) Satisfactory elemental analyses were obtained for all new compounds described here.