The formulas of the compounds indicate that there should be distinguishable "inside" and "outside" proton sites. As is observed, Ic should show two N–CH_3 resonances in the indicated configuration. The alternative hypothesis that Ic exists as a mixture of species can be rejected.[1] Steric arguments indicate that the unsymmetrical configuration is less strained than the alternate, symmetrical, structures.

The N—CH_3 resonance of Ic in H_2O–H_2SO_4 mixtures varies markedly. In water there are two, unsplit peaks. In solutions 15–60 weight per cent. in sulfuric acid the two peaks are split into doublets. This splitting is due to adjacent N–H protons as is shown by the disappearance of the doublet structure when protons are replaced by deuterons. As the concentration of acid is further increased the doublets collapse; only two broad singlets appear in 85% sulfuric acid. Above 85% sulfuric acid the singlets coalesce and a single N–CH_3 resonance is observed in "concentrated" sulfuric acid. The following scheme provides an interpretation of the data: (1) in water solution coupling between N–H and N–CH_3 protons is destroyed by rapid exchange of N–H protons with solvent; however, such exchange does not permit free rotation about C⋯N bonds; (2) at intermediate acidities the residence time of protons attached to nitrogen is long enough to allow observable spin coupling; (3) in media of high acidity proton exchange, involving formation of a second conjugate acid, again decreases the residence time of N–H protons in unique spin states; (4) finally, lifetimes of second conjugate acids become long enough to cause magnetic equivalence of N–CH_3 groups by rotation about C–$^+NH_2CH_3$ bonds.

Collapse of the two N–CH_3 doublets at intermediate concentrations of sulfuric acid is *non-simultaneous. The high field doublet collapses at lower acidities than the low field doublet,* indicating that the basicities of the two nitrogen atoms are different.

Collapse of the N–H doublet of Ia in DMSO has been studied over the temperature range 30–115°. An activation energy[2] of 7 ± 2 kcal./mole and frequency factor of 10^3–10^7 have been calculated. The similarity of these parameters to those characteristic of the collapse of the N–CH_3 doublet of N,N-dimethylformamide[3] is consistent with the view that the interconversion is accomplished by rotation about C=N bonds. Measurement of transverse relaxation times for the water resonance in dilute aqueous acid solutions of Ia shows that the mean lifetime of protons on a water molecule is directly proportional to $[H^+][H_2O]/[Ic]$. Of all mechanisms for exchange in dilute acid solution considered by Grunwald, *et al.*,[4] only the one involving hydroxide-catalyzed exchange fits this law. A reasonable value of 8×10^{10} sec.$^{-1}$ is estimated for the rate constant at 33°. Collapse of the two N–CH_3 resonances of Ic in concentrated acid was studied in concentrated D_2SO_4; $1/\tau$ is a linear function of d_0 in the D_0 interval −7.50 to −8.00, showing that protonation is responsible for exchange of the environments of the methyl groups. The rates of collapse of the two N–CH_3 doublets have been estimated in 28.4% D_2SO_4. The high field doublet was almost completely collapsed approximately 15 seconds after mixing whereas the low field doublet was almost intact. Collapse of the latter was complete within about three minutes. This observation provides a direct comparison of the rates of proton exchange at the two nitrogen atoms.

(1) The spectra could also be accounted for if the symmetrical structures were present in equal amounts, and the resonances of inside and outside N–H and N–CH_3 groups were independent of the configuration of the second nitrogen atom; an unlikely possibility.

(2) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, New York, N. Y., 1959, p. 218.

(3) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); H. S. Gutowsky, D. W. McCall and C. P. Slichter, *ibid.*, **21**, 279 (1953); W. D. Phillips, *ibid.*, **23**, 1363 (1955).

(4) E. Grunwald, A. Lowenstein and S. Meiboom, *ibid.*, **27**, 630 (1957).

(5) National Institutes of Health Predoctoral Fellow.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
(CONTRIBUTION NO. 2798) ROBERT C. NEUMAN, JR.[5]
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CALIFORNIA GEORGE S. HAMMOND
E. I. DU PONT DE NEMOURS AND COMPANY
YERKES RESEARCH LABORATORY THOMAS J. DOUGHERTY
BUFFALO 7, NEW YORK

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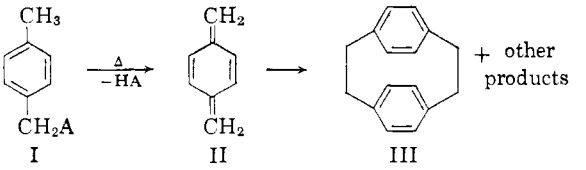
A NON-AROMATIC ROUTE TO A PARACYCLOPHANE[1]

Sir:

The strained[2] macrocyclic species [2.2]paracyclophane (III) has been prepared by three routes, each utilizing a suitable aromatic precursor. As a minor product in the pyrolysis of *p*-xylene,[3] III is isolated in *ca.* 0.3% yield employing a fast flow technique at 1065°.[4] Compound III also can be prepared (2%) by the intramolecular Wurtz-coupling[5] of 4,4′-bis-(bromomethyl)-bibenzyl, but most conveniently and in high yield (17%) by a 1,6-Hofmann elimination[6] on pyrolysis of *p*-methylbenzyltrimethylammonium hydroxide (I, A = NMe_3OH). The two pyrolytic syntheses utilize the formation of the very reactive intermediate *p*-xylylene (II).[7]



An alternative "non-aromatic" route to a *p*-xylylene and subsequently a paracyclophane can be envisioned. A four-fold elimination reaction on a judiciously chosen cyclohexane derivative would yield a tetraolefin with the requisite degree of

(1) Research supported by the U. S. Army Research Office (Durham).

(2) C. J. Brown, *J. Chem. Soc.*, 3265 (1953).

(3) C. J. Brown and A. C. Farthing, *Nature*, **164**, 915 (1949).

(4) L. A. Errede and J. P. Cassidy, *J. Am. Chem. Soc.*, **82**, 3653 (1960).

(5) D. J. Cram and H. Steinberg, *ibid.*, **73**, 5691 (1951).

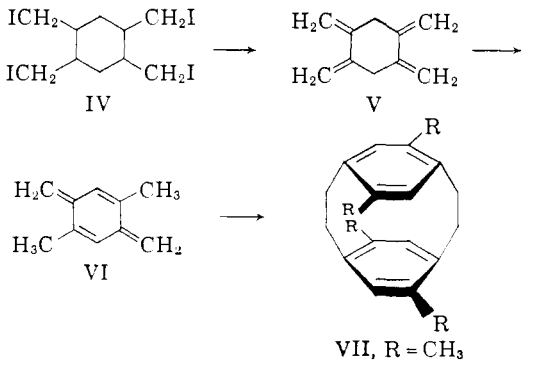
(6) H. E. Winberg, F. S. Fawcett, W. E. Mochel and C. W. Theobald, *ibid.*, **82**, 1428 (1960).

(7) The chemistry of *p*-xylylene has been reviewed recently: L. A. Errede and M. Szwarc, *Quart. Revs. (London)*, **12**, 301 (1958).

unsaturation to serve, by isomerization,[8] as a progenitor of a reactive *p*-xylylene. We wish to report the formation, in remarkably high yield, of a [2.2]paracyclophane *from a saturated aliphatic precursor*.

Treatment of 1,2,4,5-tetrakis-(tosyloxymethyl)-cyclohexane[9] with sodium iodide in acetone affords (96%) the corresponding tetraiodide IV,[10] m.p. 245–246°. Concentration of the pentane extract from the dehydroiodination of IV (potassium hydroxide in methanol, reflux six hours) gives (25%) the tetramethyl[2.2]paracyclophane VII, m.p. 104–105° after recrystallization from pentane.

Anal. Calcd. for $C_{20}H_{24}$: C, 90.85; H, 9.15; mol. wt., 264. Found: C, 90.68; H, 9.27; osmometric mol. wt., 255.



Assignment of structure VII to the hydrocarbon product is based on its chemical and spectral properties. The latter are particularly useful in that they include abnormalities previously noted as characteristic of the non-planar benzene rings in [2.2]paracyclophane.

The hydrocarbon is inert to bromine in carbon tetrachloride, permanganate solution, maleic anhydride, and cannot be reduced at room temperature and one atmosphere hydrogen pressure using either 10% palladium on carbon or Adams catalyst. The infrared spectrum of VII includes these absorption maxima ($CHCl_3$ and Nujol, cm.$^{-1}$): 3003 s (ArH); 1605 w-m,[11] 1499 m (aromatic double bond); 1374 m (CH_3); 906 s (isolated aromatic proton)[14]; and 710 s. The strong maximum at 710 cm.$^{-1}$ may be a characteristic band associated with the distorted benzene rings in the [2.2]-paracyclophane system. We[15] find this band present (725 cm.$^{-1}$, v.s.) in the parent [2.2]paracyclophane (III) and absent in both acyclic and cyclic models.[12] Both durene and biduryl exhibit only weak absorption in the region 850–600 cm.$^{-1}$.

The ultraviolet spectrum of VII is particularly revealing: $\lambda\lambda_{max}^{isooctane}$ 226, 248 sh, 287 sh and 300 sh mμ (log ε 4.20, 3.53, 2.38 and 2.31); only end absorption occurs above 320 mμ. The spectrum is virtually identical, in character and location and intensity of maxima, to that of [2.2]paracyclophane[5]: $\lambda\lambda_{max}^{cyclohexane}$ 225, 244 sh, 286 and 302 sh mμ (log ε 4.38, 3.52, 2.41 and 2.19). The spectra of both paracyclophanes are characterized by loss of fine structure, bathochromic shifts, and decreased extinction coefficients relative to both acyclic and larger cyclic models.[16] These deviations can be attributed to non-planar benzene rings[16] and have been observed in other systems.[17]

The n.m.r. spectrum[18] of VII confirms its assigned structure: τ values 3.77 singlet (ArH), 7.19 complex multiplet (CH_2) and 8.04 singlet (CH_3); integrated peak areas 1:2:3, respectively. The position of the aromatic proton absorption is significant in that it occurs outside the usual range of 2.0 to 3.5τ.[19] The corresponding absorption in [2.2]paracyclophane is similarly displaced (3.70τ),[20] while those in the isomeric dibenzocyclooctadiene (3.10τ)[21] and [2.2]metacyclophane (2.75-τ)[20] occur within the normal range.

Certain aspects concerning the formation and structure of VII are worth noting here. We view 1,2,4,5-tetramethylenecyclohexane (V) as the primary product of the dehydroiodination of IV. Under conditions utilized for the eventual isolation of product VII, it is not unlikely that V would slowly isomerize to the *p*-xylylene VI. The generation of VI at low concentrations would favor its dimerization to VII and account for the fact that only small amounts of polymeric materials are formed in the reaction.[22] Evidence for the formation of VII *via* V and VI is not compelling. That the tetraene V (or an isomeric species) is indeed formed in the reaction is evidenced by its isolation as a diadduct with maleic anhydride. The dianhydride $C_{18}H_{16}O_6$[10] has m.p. 239–240°.

We favor the stereochemistry as shown for the paracyclophane VII, with methyl groups on opposed benzene rings in non-eclipsed positions. The alternative isomer with all methyl groups eclipsed is less likely on the basis of obvious steric arguments and failure to observe spectral abnor-

(8) Calculations indicate that *p*-xylylene in the ground state has a delocalization energy of 1.93β. A high free valence index at the exocyclic carbons accounts for its high reactivity. See C. A. Coulson, D. P. Craig, A. Maccoll and A. Pullman, *Discuss. Faraday Soc.*, **2**, 36 (1947).

(9) The synthetic route to this compound, of undetermined stereochemistry, will be reported separately.

(10) Correct elemental analysis was obtained for this compound.

(11) The intensity of this maximum is significantly enhanced relative to the corresponding maxima in strainless model compounds (ref. 12). Such enhancement has been correlated with the distorted aromatic rings in paracyclophanes (ref. 5).

(12) Including durene, biduryl (ref. 13), 4,4,-dimethylbibenzyl, 1,4-bis-(2-*p*-tolyethyl)-benzene, poly-*p*-xylylene and the cyclic trimer and tetramer of *p*-xylylene.

(13) This compound, m.p. 136–137°, was obtained by Mrs. Lydia Simanyi of This Laboratory from the Grignard-coupling reaction of duryl bromide.

(14) We find this strong maximum occurs at *ca.* 880 cm.$^{-1}$ in several model compounds including durene, duryl bromide, biduryl (ref. 13), and pentamethylbenzene; it is absent in hexamethylbenzene.

(15) The previously published spectrum of III (ref. 5) covers the region 3400–870 cm.$^{-1}$.

(16) D. J. Cram, N. L. Allinger and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 6132 (1954).

(17) H. Rapoport and G. Smolinsky, *ibid.*, **82**, 1171 (1960).

(18) The spectrum was obtained at 60 megacycles in carbon tetrachloride with tetramethylsilane as internal standard. We are indebted to Dr. Eugene LeGoff and his associates at the Mellon Institute for the determination and discussion of this spectrum.

(19) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., p. 62.

(20) D. J. Wilson, V. Boekelheide and R. W. Griffin, Jr., *J. Am. Chem. Soc.*, **82**, 6302 (1960).

(21) L. A. Errede, *ibid.*, **83**, 949 (1961).

(22) The effect of monomer concentration on the competing reactions of cyclization and polymerization of *p*-xylylene has been discussed (ref. 7).

malities that would be anticipated from such serious eclipsing.

Current efforts are directed toward the elucidation of the detailed genesis of VII. These results and a full description of all products formed in the dehydroiodination of IV will be described in detail in a subsequent publication.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MICHIGAN DANIEL T. LONGONE
ANN ARBOR, MICHIGAN CHARLOTTE L. WARREN

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VINCA ALKALOIDS. XI.[1] STRUCTURES OF LEUROCRISTINE (LCR) AND VINCALEUKOBLASTINE (VLB)[2]

Sir:

The unique biological properties of leurosine and vincaleukoblastine (VLB) have been thoroughly reviewed.[3] The latter alkaloid has been introduced clinically for the treatment of Hodgkins' disease and choriocarcinoma.[4] Recently Svoboda described another alkaloid from *Vinca rosea* Linn.[5] called leurocristine (LCR) which appears to possess a different spectrum of oncolytic activity in experimental and human neoplasms.[6,7]

It is the purpose of this communication to demonstrate that LCR[5] is des-N(a)-methyl-N(a)-formyl-VLB (N(a) being the anilino-nitrogen in the vindoline moiety of the molecule), and that these compounds represent the first examples of indole-indoline alkaloids in which the indole moiety is linked through a C–C bond to the aromatic ring of the dihydroindole portion of the molecule.

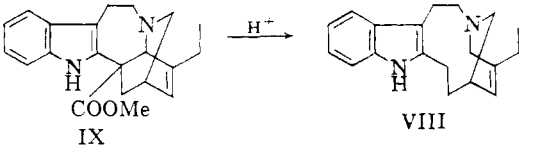
The n.m.r. spectrum of VLB, $C_{46}H_{56}O_9N_4$ (I),[8] shows these functional groups with corresponding chemical shifts: $COOCH_3$ and aromatic OCH_3 both at 3.8δ, $COOCH_3$ 3.63δ, N-CH_3 2.73δ, $OCOCH_3$ 2.12δ and NH(indole) 8.09δ. The remaining two oxygens are present as hydroxyls (free and hydrogen bonded). Their presence is easily detected in the infrared spectrum and has been substantiated by the preparation of a diacetate (ketene in benzene), $C_{50}H_{60}O_{11}N_4$[9] (II), 168–170° (dec.), $[\alpha]^{25}D$ −26.4° ($CHCl_3$). Accordingly, the n.m.r. spectrum of (II) shows three acetyl methyl peaks at 1.98, 2.09 and 2.40δ. Its comparison with the n.m.r. spectrum of VLB base indicates that the free hydroxyl (*vide supra*) is tertiary. This is apparent from the absence of a new signal in the range of 3.9–5.5δ (except for the known C-2 proton which shifts from 3.75 to 4.09δ[1], Fig. 1).

Analyses[8] of LCR base (III), sulfate and monomethiodide are consistent with a formulation of $C_{46}H_{54}O_{10}N_4$. Its ultraviolet spectrum, λ_{max}^{EtOH} 220 mμ (log a_M 4.65), 255 mμ (log a_M 4.21), 296 mμ (log a_M 4.18) and λ_{min}^{EtOH} 275 mμ (log a_M 4.02) is quite different from that of VLB and indicates a different substitution on N(a) of the dihydroindole moiety.

The infrared spectra of VLB and LCR are quite similar with the exception of the presence of a strong additional band, $\lambda_{max}^{CHCl_3}$ 5.94 μ in the spectrum of the latter. The n.m.r. spectra differ in that the N-CH_3 proton resonance at 2.73δ present in VLB is missing in LCR; and, conversely, in place of only one low field, 9.8δ proton in VLB, there are two in LCR at 9.5 and 8.9δ.

Lithium aluminum hydride reduction of the two alkaloids afforded good yields of the same[9] pentahydroxy derivative, $C_{42}H_{54}O_6N_4$[10] (IV), pK_a' 5.34 and 8.2 (33% DMF), m.p. 213–215° (dec.), $[\alpha]^{26}D$ −117.2° ($CHCl_3$). This formulation is consistent with the reduction of two methyl esters, one acetate and the N-formyl group in the case of LCR. The n.m.r. spectrum of IV shows accordingly only two methyl signals, aromatic OCH_3 at 3.8δ and N-CH_3 at 2.73δ. The position of N-CH_3 in VLB or N-CHO in LCR as well as other functional groups was demonstrated from the products of acid cleavage (concd. hydrochloric acid, $SnCl_2$, tin-metal, reflux) carried out on these alkaloids and leurosine. In each case there was obtained upon chromatography of the reaction mixture an indole compound (*vide infra*) followed by vindoline derivatives. VLB and leurosine afforded desacetylvindoline (V),[10,11] thus proving the identity of the dihydroindole portion of these alkaloids. The corresponding fraction from the cleavage of LCR yielded des-N(a)-methyldesacetylvindoline (VI), M = 400, $C_{22}H_{28}O_5N_2$. The mass spectrum as well as ultraviolet and infrared spectra demonstrate the relationship of this compound to desacetylvindoline. The structure of vindoline has been established recently,[1] and since both VLB and LCR yielded the same[10] tetracyclic indole derivative, velbanamine (VII), $C_{19}H_{26}ON_2$, m.p. 139–141°, pK_a' 8.8, $[\alpha]^{25}D$ +56.2° ($CHCl_3$), M = 298, the two alkaloids differ only in the manner mentioned above.

A related tetracyclic indole derivative, cleavamine (VIII); $C_{19}H_{24}N_2$, M = 280, m.p. 109–113°, $[\alpha]^{26}D$ +68° ($CHCl_3$), pK_a' 8.2 (33% DMF) was obtained from the cleavage of leurosine.[12] Isolation



IX VIII

(1) Vinca. X: M. Gorman, N. Neuss and K. Biemann, *J. Am. Chem. Soc.*, **84**, 1058 (1962).

(2) A.M.A.-approved generic names are vincristine and vinblastine, respectively. VLB is supplied as VELBAN® (vinblastine sulfate, Lilly).

(3) I. S. Johnson, Howard F. Wright, Gordon H. Svoboda and Janet Vlantis, *Cancer Research*, **20**, 1016 (1960).

(4) (a) M. E. Hodes, R. J. Rohn and W. H. Bond, *Canadian Cancer Conference*, **4**, 373 (1962); (b) O. H. Warwick, J. M. M. Darte and J. S. Olin, *ibid.*, 373; (c) Roy Hertz, *ibid.*, 399.

(5) G. H. Svoboda, *Lloydia*, **24**, 173 (1961).

(6) I. S. Johnson, H. F. Wright and G. H. Svoboda, *Proc. Am. Assn. for Cancer Research*, **3** (4) in press (1962).

(7) *Inter al*, J. G. Armstrong, R. W. Dyke and P. J. Fouts, *ibid.*, **3** (4), 1962 (In press).

(8) N. Neuss, M. Gorman, G. H. Svoboda, G. M. Maciak and C. T. Beer, *J. Am. Chem. Soc.*, **81**, 4754 (1959). In view of the new chemical evidence we prefer the present formula over $C_{46}H_{58}O_9N_4$ reported therein. Satisfactory analyses were obtained on all compounds for which empirical formulas are given.

(9) Identity was established by the comparison of m.p., X-ray powder patterns and infrared spectra in chloroform solution.

(10) N. Neuss, M. Gorman and G. H. Svoboda, Plant Chemists Meeting, Columbia University, February 12, 1960, New York, N. Y.

(11) Desacetylvindoline is obtained from vindoline by a mild hydrolysis, M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes and N. J. Cone, *J. Am. Pharm. Assn. Sci. Ed.*, **48**, 256 (1959).

(12) The correct formula of leurosine is still in doubt because of difficulty of preparing a solvent free sample.