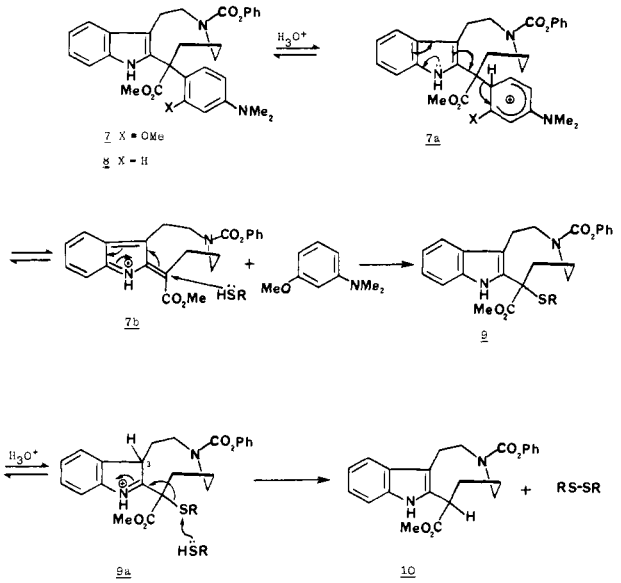
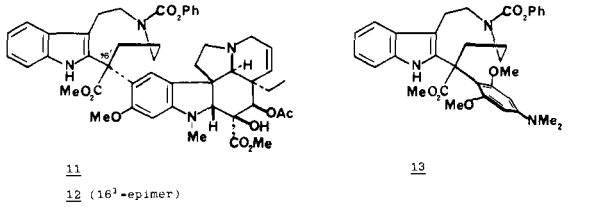


BuSH/MeOH at 65 °C lead directly to the reduced adduct **10** in 89% yield. It was predicted that the *des*-methoxy dimer **8**, which is less electron-rich, would be inert to the above ipso protonation conditions, and this indeed is the case. The reduction product **10** presumably arises from C-3 protonation of **9** to give **9a**, which is now an activated sulfenylating species. Thiol attack at sulfur on **9a**, followed by prototropic shift, gives the reduction product **10** and the disulfide.[12] When **9** (R = CH_2Ph) was treated with $PhCH_2SH$ (2.0 equiv)/HBF_4 aqueous THF it gave **10** (69%) and dibenzyldisulfide (94% based upon **9**). In contrast, **9** (R = CH_2Ph) on exposure to HBF_4/aqueous THF gave dibenzyldisulfide (96%, based upon **9**), and *no* reduction product **10**. [$PhCH_2SH$ gave dibenzyldisulfide (18%) when treated with HBF_4/aqueous THF.][13] The bis indole alkaloid model **11** (natural configuration at C-16[1]) on treatment with aqueous TFA/*n*-BuSH/26 °C gave vindoline **3** (60%) and the reduction product **10** (41%). Similarly, **11** gave vindoline **3** (65%), $(PhCH_2S)_2$



(43%), **9** (R = CH_2Ph) (13%), and **10** (50%), when exposed to aqueous HBF_4/THF/$PhCH_2SH$/20 °C. Interestingly, the bis indole alkaloid model **12** (16[1]-epimer) gave vindoline **3** (40%), and no other identifiable fragments, when exposed to the above conditions.

Vinblastine itself could be cleaved with HCl (12 M)/*n*-BuSH to give 4-deacetylvindoline, but no identifiable products from the top half.[14]

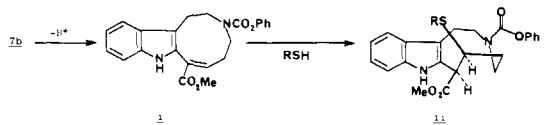
To illustrate that the more susceptible the bottom half of the bis alkaloids are to ipso protonation the more readily they are cleaved, we treated the *m,m*-dimethoxy analogue **13** with vindoline **3**/aqueous TFA/THF at 25 °C for 52 h and isolated **11**/**12** (ca. 1:1) in 24% yield.

The acid-promoted cleavage of the model bis alkaloid **7**, subsequent iminium ion **7b** thiol trapping, and eventual reductive cleavage provide an interesting prediction. There could be a biological difference between **7** and **8**, since only **7** can produce **7b**. It turns out that **7** is weakly cytotoxic, whereas **8** is not.[15] While this does not in anyway necessarily corroborate the mechanistic hypothesis, it is nevertheless provocative. The specific acidic conditions used to generate **7b** in no way represent so-called physiological conditions, but the exemplary ability of enzymes to lower $\Delta G^{\ddagger}$ could overcome this problem.

The above hypothesis may be useful in explaining the in vivo biological and pharmacological properties of bis alkaloids and for designing new drugs based upon natural bis alkaloids.[16]

Acknowledgment. The National Institutes of Health is thanked for financial support. Drs. Homer Pearce and Jeffry Howbert (Eli Lilly Research Laboratories) are thanked for information concerning vinblastine, for supplies of vinblastine and vindoline, and for screening relevant compounds.

(12) If **9** were to reverse to **7b**, this intermediate should undergo proton loss to give the α,β-unsaturated ester i, which would subsequently conjugatively add RSH to give the adduct ii. We have made i, and it is not formed (nor ii) when **9** is exposed to RSH/H^+.



(13) The amount of dibenzyl disulfide produced in the cleavage reaction approximately corresponds to the amount of reduction to give **10**.

(14) We would have expected to isolate **4** or **5**. Although it should be noted that the original $Sn/SnCl_2$ cleavage of **1** only gave **5** in very low yields.[8]

(15) **7** has a CEM IC 50 4.3 μg/mL, whereas **8** > 20.

(16) Vincristine **2** should not undergo reductive cleavage. N^1-Formyl-6,7-dihydro-16-methoxytabersonine does not undergo the Potier coupling reaction (see ref 10).

Conformationally Dependent Intrinsic and Equilibrium Isotope Effects in *N*-Methylpiperidine

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Conformational equilibrium isotope effects (CEIE)[1] have recently been shown to differ substantially between cyclohexane, where deuterium in a CHD group prefers the equatorial over the axial position by 6.3 ± 1.5 cal/mol,[2] and 5,5-dimethyl-1,3-dioxane-2-d_1, where the CHD lies between two oxygen atoms and deuterium prefers the equatorial position by 49 ± 3 cal/mol.[3] Anet and Kopelvich attributed the difference primarily to n-σ^* (negative) hyperconjugation which weakens and lengthens the bond to an axial substituent that is anti to a lone electron pair.[3] Until their observation, there had been little experimental evidence for the predicted angular dependence of the energetic consequences of negative hyperconjugation.[4,5] We now report an even larger CEIE in *N*-methylpiperidine and also report a substantial difference in the *intrinsic* isotope effect on the ^{15}N chemical shift

(1) Baldry, K. W.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1663.

(2) (a) The quoted value is derived from measurements on cyclohexane-d_{10}: Anet, F. A. L.; Kopelvich, M. *J. Am. Chem. Soc.* **1986**, *108*, 1355. (b) Another value of about 50 cal/mol was derived from earlier measurements on cyclohexane-d_1: Aydin, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 985.

(3) Anet, F. A. L.; Kopelvich, M. *J. Am. Chem. Soc.* **1986**, *108*, 2109.

(4) Previous evidence is based on "Bohlmann" bands for amines in infrared spectroscopy, e.g.: (a) Bohlmann, F. *Ber.* **1958**, *91*, 2157. (b) Hamlow, H. P.; Okuda, S.; Nakagawa, N. *Tetrahedron Lett.* **1964**, 2553. (c) Krueger, P. J.; Jan, J. *Can. J. Chem.* **1970**, *48*, 3229, 3236.

(5) Theoretical studies: (a) DeFrees, D. J.; Bartmess, J. E.; Kim, J. K.; McIver, R. T., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6451. (b) DeFrees, D. J.; Hehre, W. J.; Sunko, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 2323. (c) DeFrees, D. J.; Taagepera, M.; Levi, B. A.; Pollack, S. K.; Summerhays, K. D.; Taft, R. W.; Wolfsberg, M.; Hehre, W. J. *J. Am. Chem. Soc.* **1979**, *101*, 5532. (d) Pross, A.; Radom, L.; Riggs, N. V. *J. Am. Chem. Soc.* **1980**, *102*, 2253. (e) Pross, A.; DeFrees, D. J.; Levi, B. A.; Pollack, S. K.; Radom, L.; Hehre, W. J. *J. Org. Chem.* **1981**, *46*, 1693. (f) Schleyer, P. v. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141.

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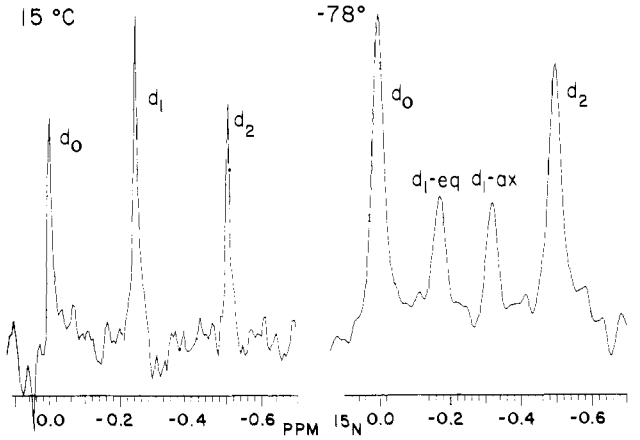

Figure 1. Natural abundance $^{15}N(^1H)$ NMR spectra at 30.4 MHz of mixtures of *N*-methylpiperidine with the *2-d*$_1$ and *2,2-d*$_2$ isotopomers in $CFCl_3$ at 15 and −78 °C. Spectra were acquired with a spectral width of 345 Hz, 2752 data points, pulse repetition rate of 4 s, 75° pulse width, sensitivity-enhancing weighting function giving line broadening of 0.3 Hz, continuous high-power broadband ^1H decoupling, no lock, phase-corrected signals, and a total of about 1000 transients.

due to axial and equatorial deuterium at neighboring carbons.

N-Methylpiperidine can readily be observed by NMR under conditions of both fast and slow exchange between chair conformers in which the *N*-methyl group remains equatorial. The exchange occurs via nitrogen inversion (low barrier) and ring reversal (E_a = 14.4 kcal/mol).[6] The axial *N*-methyl contributes little to the equilibrium ($\Delta G° \simeq 2.5$ kcal/mol).[7]

Figure 1 shows the effect on the ^{15}N NMR spectrum of lowering the temperature for a mixture of unlabeled *N*-methylpiperidine and the *2-d*$_1$ and *2,2-d*$_2$ isotopomers.[8] At 15 °C, a single averaged ^{15}N signal is seen for the *2-d*$_1$ compound which has an upfield intrinsic NMR isotope shift, $^2\Delta N(2\text{-}d_1)$, relative to the unlabeled compound of −0.242 ± 0.004 ppm.[9] The $^2\Delta N(2,2\text{-}d_2)$ is −0.505 ± 0.004 ppm, slightly more than twice the effect of a single deuterium. At −78 °C, separate ^{15}N signals are seen for *2-d*$_1$(ax) and *2-d*$_1$(eq), with respective isotope shifts of −0.319 and −0.175 ± 0.010 ppm. The $^2\Delta N(2,2\text{-}d_2)$ remains −0.506 ppm at −78 °C. Similarly, at −78 °C a signal is observed for the axial–axial combination of deuteriums in the *cis-2,6-d*$_2$ isotopomer and another for the equatorial–equatorial conformer, with isotope shifts of −0.644 and −0.352 ± 0.010 ppm, respectively. The *trans-2,6-d*$_2$ isotopomer gives only one ^{15}N signal with an isotope shift of −0.500 ppm, halfway between the two signals for the *cis-2,6-d*$_2$ isotopomer. The intrinsic effect of an axial deuterium on the ^{15}N shift is nearly twice that of an equatorial deuterium.

The isotope shifts at ^{15}N are intrinsic and *not* the result of an equilibrium isotope effect such as the perturbation of an equilibrium between axial and equatorial *N*-methyl conformers. This is clearly shown by 75.43-MHz ^{13}C NMR spectra which do not show the temperature dependent changes in isotope shifts which would be expected if an isotope effect were perturbing an equilibrium involving another species. The small intrinsic shifts, $^n\Delta C$,

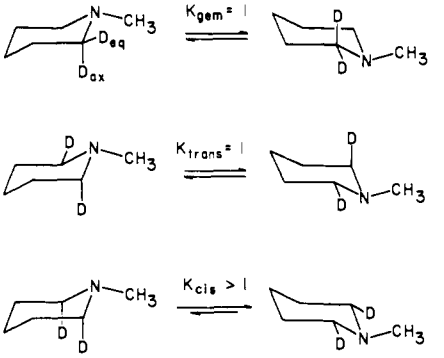

Figure 2. Equilibria in d_2-isotopomers of *N*-methylpiperidine.

are very similar to those in cyclohexane.[10,11] Axial and equatorial deuterium at C_2 produce the *same* intrinsic shift at C_3 of −0.109 ± 0.010 ppm.[10] Thus, it is also clear that the conformationally dependent isotope shifts at nitrogen must result from an angularly dependent interaction of the C–H(D) bonds with the lone pair, since there is no angular dependence of the isotope shifts at C_3.

On the other hand, there is a CEIE on the distribution of deuterium between equatorial and axial positions. The chair–chair equilibrium is degenerate (Figure 2) for the *2,2-d*$_2$ and *trans-2,6-d*$_2$ isotopomers, but the equilibrium is perturbed toward equatorial placement of the deuterium for the *2-d*$_1$ and *cis-2,6-d*$_2$ isotopomers. The perturbed equilibrium is manifested in several NMR measurements, which vary in their suitability for precise quantitative determination of the small isotope effect. In ^{15}N spectra under fast exchange at 20°, the effect of deuteriation at C_2 is nonadditive, i.e., the $^2\Delta N(2\text{-}d_1)$ is slightly less than half the $^2\Delta N(2,2\text{-}d_2)$. The nonadditivity reflects the greater proportion of the *2-d*$_1$(eq) conformer which has the smaller intrinsic effect at nitrogen. However, the deviation from additivity is too small for precise measurement of the CEIE.[12] Similarly, a difference of about 0.02 ppm is expected between ^{15}N signals for the *trans-2,6-d*$_2$ and *cis-2,6-d*$_2$ isotopomers at 20°, but the difference could not be resolved. When exchange is slow at −78°, direct integration of ^{15}N, ^2H, and ^1H signals for the *2-d*$_1$ and *cis-2,6-d*$_2$ isotopomers also show qualitatively the preference for equatorial deuterium.

The most precise measurement of the CEIE comes from the signal separation between the averaged signal for the *trans-2,6-d*$_2$ isotopomer and the averaged signal for the *cis-2,6-d*$_2$ isotopomer in the rapid exchange ^2H spectrum at 19.5°. The signal position for *trans-2,6-d*$_2$ is the average of the chemical shifts for equatorial and axial deuterium, but the signal for *cis-2,6-d*$_2$ is shifted 0.051 ± 0.003 ppm to lower field because of the greater proportion of the conformer with both deuteriums equatorial. A temperature independent chemical shift difference of 0.976 ± 0.006 ppm is found between axial and equatorial (deshielded) deuterium in low-temperature spectra. The calculated value for the equilibrium at 19.5° is K_{cis} = 1.234 ± 0.018, which corresponds to $\Delta G°$ = 122 ± 8 cal/mol or 61 cal/mol per deuterium. This agrees with a value of $\Delta G°$ = 63 ± 12 cal/mol we obtain by Saunders' procedure[13] from the separation of signals for hydrogens at C_6 in the rapid exchange ^1H spectrum of the *2-d*$_1$ isotopomer.[14]

(6) Lambert, J. B.; Oliver, W. L., Jr.; Packard, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 933.

(7) For a recent discussion, see: Profeta, Jr., S.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907, and references therein.

(8) (a) Spectra of $CFCl_3$ solutions were measured on a Varian XL-300 NMR spectrometer at 30.41 MHz for ^{15}N, 75.43 MHz for ^{13}C, 46.04 MHz for ^2H, and 300.00 MHz for ^1H. Resolution enhancing weighting functions and zero-filling of the FID were applied in the analysis of some spectra. (b) *N*-Methylpiperidine-*2-d*$_1$ was synthesized from 2-bromopyridine by conversion to pyridine-*2-d*$_1$ with Zn/D_2SO_4, quaternization with CH_3I, and hydrogenation over PtO_2. *N*-Methylpiperidine-*2,2-d*$_2$ was obtained from $LiAlD_4$ reduction of *N*-methyl-2-piperidone. A 2:1 cis/trans mixture of *N*-methylpiperidine-*2,6-d*$_2$ isotopomers was obtained by OD^-/D_2O exchange of *N*-methylpyridinium iodide, followed by hydrogenation over PtO_2.

(9) The notation $^n\Delta X(Y)$ indicates the incremental change in the chemical shift of nucleus X induced by substitution by the heavy nucleus Y at a distance of *n* bonds from X. We define upfield isotope shifts to be negative, following the usual convention for substituent effects on chemical shifts.

(10) Observed isotope shifts for the *2,2-d*$_2$ isotopomer at 20 °C: $^1\Delta C_2$ = −0.855, $^2\Delta C_3$ = −0.218, $^3\Delta C_4$ = −0.049, $^3\Delta C_6$ = −0.038, $^3\Delta CH_3$ = −0.064, $^4\Delta C_5$ = 0.000 ± 0.005 ppm. These values are about twice those for cyclohexane-*d*$_1$.[11] At −78 °C, ^{13}C spectra of the *cis-2,6-d*$_2$ and *trans-2,6-d*$_2$ isotopomers with the unlabeled compound show no difference for axial and equatorial alignments of deuterium in the effect at C_3 ($^2\Delta C_3$ = −0.109 ppm).

(11) (a) Aydin, R.; Günther, H. *J. Am. Chem. Soc.* **1981**, *103*, 1301. (b) Aydin, R.; Wesener, J. R.; Günther, H.; Santillan, R. L.; Garibay, M.-E.; Joseph-Nathan, P. *J. Org. Chem.* **1984**, *49*, 3845.

(12) The difference between the observed $^2\Delta N(2\text{-}d_1)$ of −0.242 ppm and the expected value of −0.252 based on additivity is 0.010 ± 0.006 ppm. To obtain proportions of conformers from this difference requires the individual isotope shifts for the *2-d*$_1$(eq) and *2-d*$_1$(ax) conformers; these are less precise (±0.010 ppm) because of the broader line widths at −78 °C.

(13) (a) Saunders, M.; Jaffe, M. H.; Vogel, P. *J. Am. Chem. Soc.* **1971**, *93*, 2558. (b) Saunders, M.; Telkowski, L.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8070.

The CEIE of 61 cal/mol per deuterium in *N*-methylpiperidine can be entirely accounted for, within the error limits, by zero-point energy contributions associated with the C–H stretching frequencies. In the infrared, C–D stretching bands occur at 2050 (ax) and 2160 (eq) cm^{-1} for *N*-alkylpiperidines,[15] a difference of 110 cm^{-1}, corresponding to a predicted isotope effect of about 55 cal/mol.[16] The CEIE may be compared with a CEIE of 25 cal/mol per deuterium and *per oxygen atom* in the 1,3-dioxane examined by Anet and Kopelvich,[3] which was also largely accounted for by stretching vibrations although an opposing contribution from bending vibrations was needed. The larger CEIE in *N*-methylpiperidine is consistent with the theory of negative hyperconjugation, since a high-lying σ^* orbital should interact more with a nonbonding orbital for nitrogen than with a lower lying oxygen nonbonding orbital. The angular dependence of the intrinsic effect is also consistent with negative hyperconjugation, wherein isotopic perturbation of a C–H bond anti to the lone pair should have a greater effect on the ^{15}N shielding than perturbation of a gauche C–H bond because of a greater effect on the vibrationally averaged electron distribution around nitrogen.[17,18]

(14) The ^1H spectrum was obtained with specific decoupling from the $C_{3,5}$ hydrogens. The C_6 hydrogens give separate signals, but one overlaps with the signal of the remaining C_2–H, thereby introducing some uncertainty in shift and error in K and $\Delta G°$. The observed separation of signals was 0.053 ppm at 19.5°, and the difference in axial and equatorial ^1H shifts from low-temperature spectra is 0.976 ppm.

(15) Tsuda, M.; Kawazoe, Y. *Chem. Pharm. Bull.* **1968**, *16*, 702.

(16) Calculated from the difference in the sum of C–H and C–D stretching frequencies for the 2-d_1(ax) and 2-d_1(eq) isotopomers, based on the assumption that ν_{CH}/ν_{CD} is about 1.35.

(17) For a discussion of intrinsic isotope shifts at ^{13}C and ^{19}F associated with negative hyperconjugation in carbanions and anilines, see: Forsyth, D. A.; Yang, J.-R. *J. Am. Chem. Soc.* **1986**, *108*, 2157.

(18) For an earlier suggestion of an effect on ^{15}N shifts due to delocalization of the lone pair to antiperiplanar C(α)H bonds, see: (a) Duthaler, R. O.; Williamson, K. L.; Giannini, D. D.; Bearden, W. H.; Roberts, J. D. *J. Am. Chem. Soc.* **1977** *99*, 8406. (b) Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3882.

*Book Reviews**

Stereoselective Synthesis. By Mihaly Nogradi (Technical University, Budapest). VCH Publishers: New York. 1987. xiv + 356 pp. $97.50. ISBN 0-89573-494-X

This is a well-written monograph dealing with the currently very active area of stereoselective syntheses. The book contains many references, but it is quite readable for students and others who wish to acquaint themselves with this very important subject. There is a good discussion of terminology, principles, and concepts in the first chapter of the book. The next chapters (8 in all) deal with practical synthetic aspects of asymmetric syntheses and review the major accomplishments over the past 15 years or so. A number of tables accompany the discussion showing yields, ee's, etc. In effect, the book reiterates what is now in the five-volume treatise "Asymmetric Synthesis" edited by J. D. Morrison. However, this is a transportable version and will inform the reader quite adequately about details on these major synthetic accomplishments. In addition to asymmetric synthetic methods, which the author confesses he is biased toward, there are numerous discussions on related enantioselective processes and sufficient mechanistic aspects to allow the reader adequate comprehension of the reactions in question.

The major stereochemical processes are covered (except enzyme-mediated reactions), which include catalytic hydrogenation, both homo- and heterogeneous, non-catalytic reduction involving chiral boranes, metal hydrides, NADH mimics, etc., as well as oxidations with chiral auxiliaries or catalysts. The major portion of the book deals with asymmetric C–C bond-forming reactions, which in the biased opinion of this reviewer is of the utmost importance. The "aldol" process, in its broadest terms, is covered and summarized quite well as is the asymmetric nucleophilic and electrophilic C–C bond-forming reactions. Pericyclic reactions of all types are addressed showing the growing importance of this process in C–C bond-forming reactions. Finally, a few pages dealing with stereoselective C-hetero bonds, including protonation of chiral carbanions, are included.

In summary, the author has made a valiant attempt to cover a vast and rapidly growing field of organic chemistry in under 400 pages, but to this reviewer's surprise, he has succeeded far beyond my expectations. By brisk and clear writing, and clearly drawn and aesthetically pleasing structures, the topic is quite easily read by experts and students alike. To be sure, many topics are scanned over quickly, but the essence is always present. This is a rather good book on which a course could be based because it leaves the instructor to fill in some of the depth omitted by the author. The only negative comment that can be made is the exorbitant cost of the book, which will, unfortunately, put it out of the range of those who can benefit by it most.

A. I. Meyers, *Colorado State University*

Residue Reviews. Volume 97. Edited by F. A. Gunther and J. D. Gunther. Springer-Verlag: Berlin and New York. 1986. 151 pp. $33.50. ISBN 0-387-96294-8

This is the last volume to be edited by its founder, Francis Alan Gunther, who died in 1985. The series is to be continued, but under the new title *Reviews of Environmental Contamination and Toxicology*. This volume begins with an appreciation of Gunther's contributions to pesticide chemistry.

Five reviews make up this volume, as follows: Regulatory aspects of bound residues (chemistry); 1,3-Dichloropropene; Postharvest fungal decay control chemicals; Effects of synthetic pyrethroid insecticides on nontarget organisms; Toxicology of methyl ethyl ketone.

The subject index is thorough.

Reviews of Environmental Contamination and Toxicology. Volumes 98 and 99. Edited by G. W. Ware. Springer-Verlag: Berlin and New York. 1987. Volume 98: 166 pp. $39.00. ISBN 0-387-96448-7. Volume 99: 175 pp. $41.00. ISBN 0-387-96498-3

These are the first and second volumes under the new Editor of the series that is a continuation of *Residue Reviews*. The nine reviews in them are as follows: Attenuation of polychlorinated biphenyls in soils; Maleic hydrazide residues in tobacco and their toxicological implications; Fate and persistence of aquatic herbicides; Organophosphorus pesticide residues in fruits and vegetables; Biological half-lives of chemicals in fishes; Propylene chlorohydrins: toxicology, metabolism and environmental fate; The pyrolysis of cannabinoids; Pesticide fate from vine to wine; Transport and transformations of organic chemicals in the soil–air–water ecosystem. The review on wine in Volume 99 is recommended to a much wider audience than just pesticide chemists. The happy conclusion is that pesticide concentrations are so highly diminished in the wine-making process that no significant toxic or organoleptic effects are to be found, but nevertheless, the knowledge that a wine began its career with grapes treated with "mancozeb", "furolaxyl", and other substances with cacophonic names cannot but reduce the romantic aspects of wine appreciation.

The Editor has included a short chapter of information for prospective authors of reviews, in which he bravely offers his home telephone number as well as that of his office. It is slightly disappointing to read in this chapter that Chemical Abstracts index terms, which are designed for

*Unsigned book reviews are by the Book Review Editor