High-Resolution Mass Spectra of Ajmaline and Related Alkaloids[1,2]

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The mass spectra of ajmaline (I) and a series of derivatives, such as 21-deoxy, 17-epi, 17-keto, 19,20-dehydro, and 2-epi analogs, as well as others having additional substituents at C-16 or in the benzene ring, have been determined. The fragmentation processes, some of which are very sensitive to subtle structural changes (e.g., epimerization at C-2), are discussed in the light of more precise data obtained with a double-focusing mass spectrometer.

As part of a systematic study of the mass spectra of alkaloids[3] and during the course of the determination of the structure of quebrachidine[4] we determined the mass spectra of a series of compounds related to ajmaline (I), the major alkaloid of *Rauwolfia serpentina* Benth. The availability of a number of derivatives of this alkaloid[5] such as 21-deoxy analogs, 17-ketones (e.g., ajmalidine, V), 19,20-dehydro derivatives (e.g., tetraphyllicine, IV) as well as epimers at the C-2, C-17, or C-21 position provided an interesting set of compounds possessing the same carbon skeleton but differing in rather subtle details which in some instances do and in others do not change the fragmentation of the molecule as shall be shown below.

The earlier part of this study[3,4] made use of conventional mass spectra obtained with a single focusing spectrometer and this work has more recently been augmented by the determination of the accurate masses of all ions produced from these compounds on electron impact using a high-resolution mass spectrometer of the Mattauch–Herzog type. These data permit a much more detailed and better supported interpretation than earlier studies of the mass spectra of alkaloids in which single-focusing instruments were employed.

As implied in previous brief communications on some of the aspects of this work,[3,4,6] the mass spectra of ajmaline derivatives fall into three general groups, namely, those that are similar to the mass spectrum of ajmaline (I, Fig. 1) itself, those that possess a 17-ketone group and differ considerably in mass spectrometric behavior from ajmaline but are very similar to the spectrum of ajmalidine (V),[6] and finally those differing in the stereochemistry at C-2, which again greatly alters their fragmentation behavior as illustrated by the spectrum of quebrachidine (X).[4] The mass spectral characteristics of these three groups shall be outlined below along with proposals for the course of the fragmentation deduced from the high-resolution mass spectra of these compounds.

The mass spectrum of ajmaline (I) is plotted in Fig. 1 as recorded with a conventional single-focusing spectrometer except that the elemental composition, deduced from accurate mass measurements with a high-resolution spectrometer, has been added for those peaks whose

characteristics will be discussed below. In this and all following figures, the values in brackets after the elemental composition indicate the relative intensity of components forming a multiplet. It should also be noted that to simplify the figures the elemental composition of species attributed to a ^{13}C-containing analog of the ion 1 mass unit lower is not listed.

The conventional mass spectrum of I itself has been published recently[7] and the interpretations put forward agree for the most part with ours, except for some of the components of those peaks which the high-resolution spectrum revealed to be multiplets and for some of the generalizations implied in that paper and derived from the spectrum of a single representative (I) of this group. That these do not hold we have pointed out already in connection with our studies on ajmalidine.[6]

The loss of 15 and 18 mass units are, as expected, attributed to loss of a methyl group and water, respectively. The loss of 29 mass units involves, however, for the most part the loss of CHO and only little loss of C_2H_5 which was formerly[7] thought to be exclusively responsible for the peak at m/e 297. The elimination of an aldehyde group is at first surprising but seems to be caused by the existence of ajmaline in the gas phase partly as the open aldehyde form Ia. That it is mainly the oxygen at C-21 which is lost is supported by the spectrum (Fig. 2) of 21-deoxyajmaline (II) in which the M − 29 peak is, in contrast to the spectrum of I, about equally attributed to loss of ethyl and loss of CHO. The latter must represent C-17, involving a more complex rearrangement to a dihydroindole C-17 aldehyde.

Various aspects of the ajmaline spectrum (Fig. 1) point to an electron-impact-induced cleavage of the five-membered ring with migration of the *cis*-hydrogen from C-2 to C-17 and formation of a carbon skeleton (Ib) of the sarpagine type. Two independent facts

(1) Paper XXII on the "Application of Mass Spectrometry to Structure Problems."

(2) Paper XXI: K. Biemann, P. Bommer, and D. M. Desiderio, *Tetrahedron Letters*, **No. 26**, 1725 (1964).

(3) A. L. Burlingame, Ph.D. Thesis, M.I.T., 1962.

(4) M. Gorman, A. L. Burlingame, and K. Biemann, *Tetrahedron Letters*, **No. 1**, 39 (1963).

(5) For leading references to the structures of the compounds see M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962).
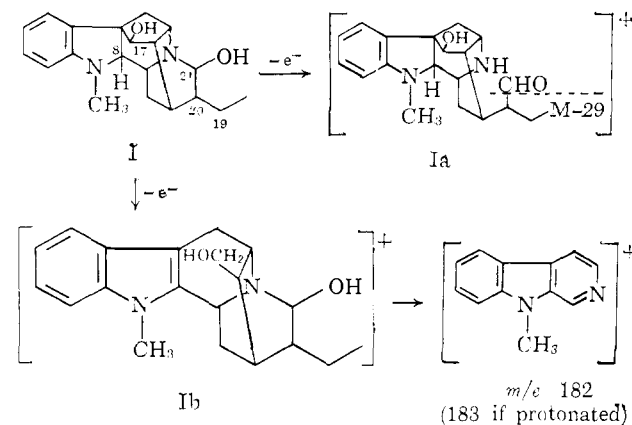
(6) K. Biemann, P. Bommer, A. L. Burlingame, and W. J. McMurray, *Tetrahedron Letters*, **No. 28**, 1969 (1963).

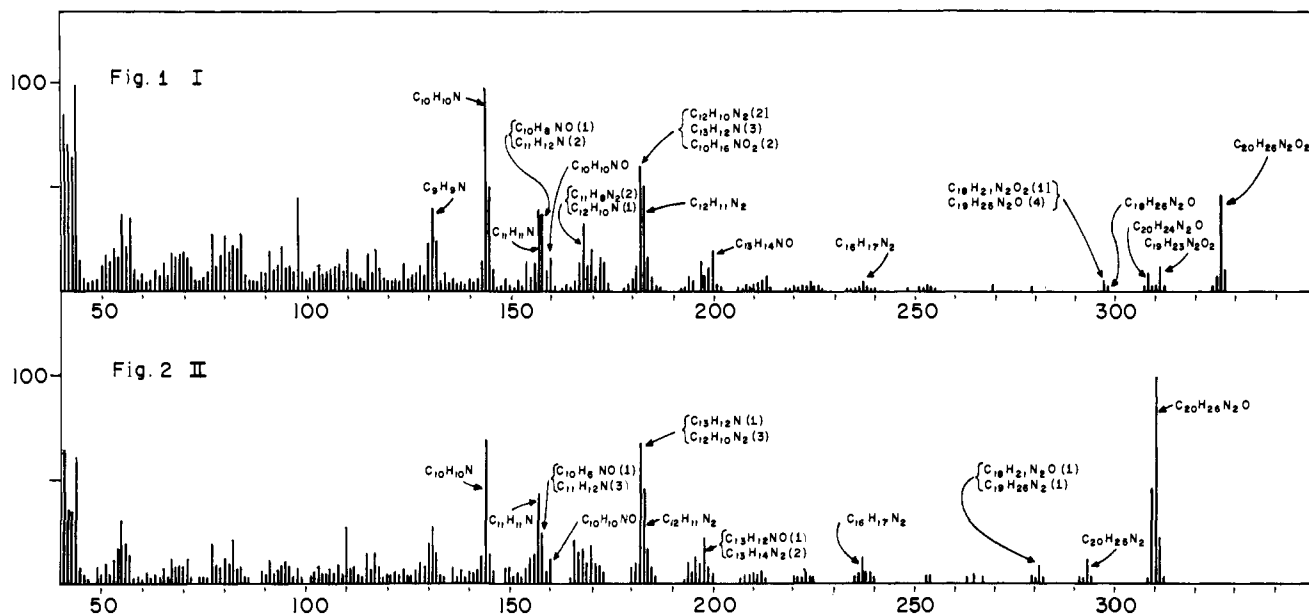(7) G. Spiteller and M. Spiteller-Friedmann, *ibid.*, **No. 3**, 147 (1963).

Fig. 1.—Mass spectrum of ajmaline (I).
Fig. 2.—Mass spectrum of 21-deoxyajmaline (II).

support this proposal. First, as previously noted,[7] some features of the spectrum of ajmaline resemble the mass spectrum of sarpagine,[8] namely the intense peaks at m/e 182 and 183. Second, these peaks are absent in the mass spectra of the 2-epi series, as will be discussed below, presumably because there the hydrogen atom at C-2 is *trans* with respect to C-17. This rearranged form of the molecular ion may now eliminate C-14, 15, 16, and 17 as well as the 21-substituent (OH) to form the $C_{16}H_{17}N_2$ ion at mass 237, or to lose in addition C-18, 19, 20, and 21, with or without rearrangement of a hydrogen to N-4, to form the $C_{12}H_{10}N_2$ and $C_{12}H_{11}N_2$ ions at m/e 182 and 183, respectively. Mechanisms for these fragmentation processes have been suggested previously in connection with a discussion of the sarpagine carbon skeleton.[8]

The unexpected feature of the peak at mass 182 is its multiplicity that was observed when determining the spectrum with a double-focusing mass spectrometer which showed the presence of a species containing only one nitrogen atom ($C_{13}H_{12}N$) as well as $C_{10}H_{16}NO_2$ in addition to the β-carboline ion $C_{12}H_{10}N_2$. Mass 183 is, however, attributed only to the β-carbolinium ion $C_{12}H_{13}N_2$ aside from a minor contribution from the ^{13}C analogs of the species of m/e 182.

The formation of a second, major species of m/e 182 outlined below is supported by the elemental composition ($C_{13}H_{14}NO$) of the ion of mass 200, which, while of relatively low abundance, suggest a genesis analogous to the one of the intense peak at m/e 198 in the spectrum of ajmalidine. It is the reason why that spectrum is so surprisingly different from the one of ajmaline, as has been pointed out earlier.[7] Unlike that ion, the analogous one (m/e 200) from ajmaline (I) is able to decompose further by elimination of the 17-hydroxyl as H_2O which leads to the carbazolinium ion $C_{13}H_{12}N$, a process resulting in a decrease of intensity of mass 200 in favor of an increase at mass 182.

The third of the 182-triplet has a high H:C ratio indicating a nonaromatic species which we attribute

(8) K. Biemann, *J. Am. Chem. Soc.*, **83**, 4801 (1961).

m/e 200 ($C_{13}H_{14}NO$) m/e 182 ($C_{13}H_{12}N$)
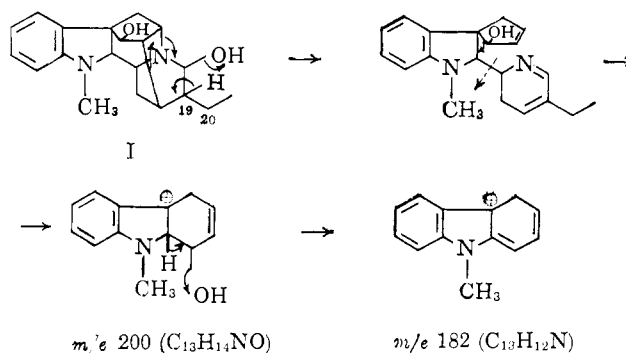
to a small contribution by a process that becomes the major one in the 2-epi series (*e.g.*, IX–XII), namely, the cleavage of the 2,3- and 7,17-bond with simultaneous aromatization of ring B and formation of a 3,17-bond, followed by rupture of the 5,6-bond (see below, genesis of m/e 166 for IX).

The peaks at m/e 144 and 157 ($C_{10}H_{10}N$ and $C_{11}H_{11}N$) correspond to the N-methylindole system with one (probably C-6) or two (probably C-5 and 6) additional carbon atoms. These are typical fragments of N-methyl-substituted indole alkaloids.[9] In the presentation typical of conventional mass spectra the peak at m/e 158 does not appear to be characteristic. The high-resolution spectrum reveals, however, an otherwise unsuspected significance as it is a doublet consisting not only of $C_{11}H_{12}N$ (the specie containing one hydrogen atom more than m/e 157) but also of $C_{10}H_8NO$. The latter requires retention of the oxygen at 17 and thus also C-17. The presence of the $C_{11}H_{12}N$–$C_{10}H_8NO$ doublet is thus an indication of this type of indole alkaloid possessing a C-7, C-17 bond and an oxygen atom at C-17. It is, in fact, found in all ajmaline derivatives of that type which we have investigated and it should be noted that those bearing a 17-hydroxyl also exhibit an appreciable peak at m/e 160, attributed to $C_{10}H_{10}NO$ which is absent in the 17-keto

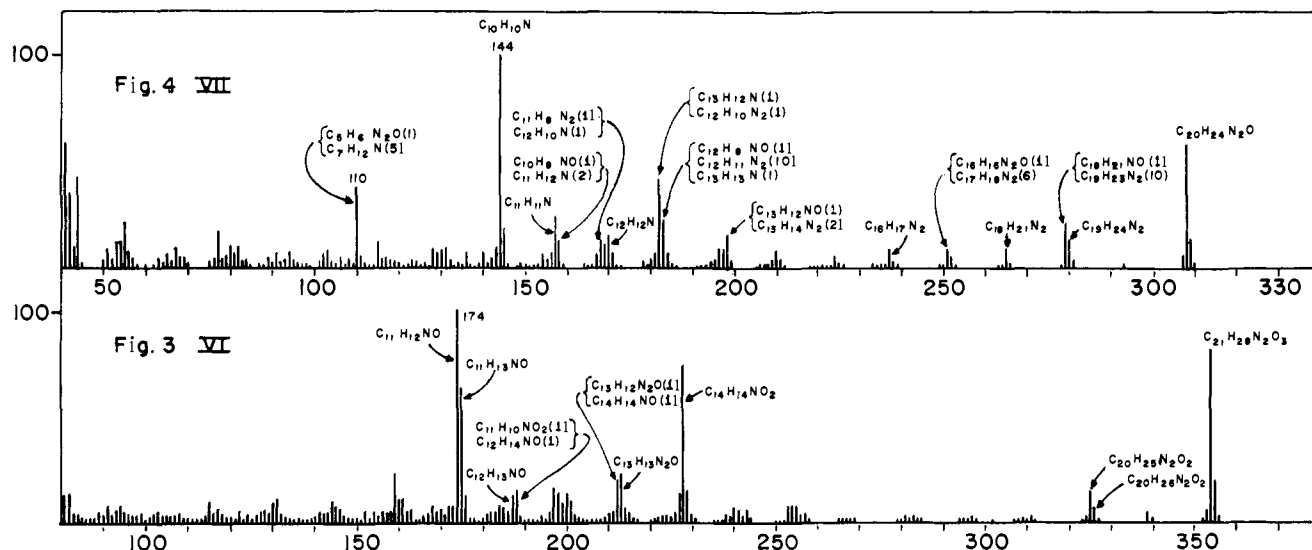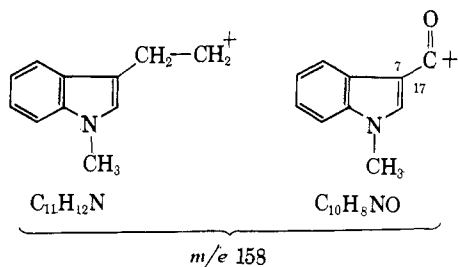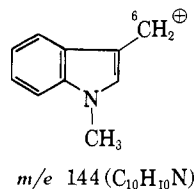(9) For a summary see K. Biemann, "Mass Spectrometry," McGraw–Hill Book Co., Inc., New York, N. Y., 1962.

Fig. 3.—Mass spectrum of vomalidine (VI).
Fig. 4.—Mass spectrum of 21-deoxyajmalone (VII).

derivatives. For any analogs unmethylated at N-1 (e.g., IX and X[4]) this ion loses, of course, CH_2 and appears at m/e 144.

m/e 144 ($C_{10}H_{10}N$)

$C_{11}H_{12}N$ $C_{10}H_8NO$

m/e 158

Various slight changes such as epimerization at C-20 or removal of the 21-hydroxyl group, epimerization of the 17-hydroxy group, or unsaturation in the C_2-side chain have no effect on the basic fragmentation processes which were outlined for ajmaline above. Thus the mass spectrum[3] of isoajmaline (the 20-epimer) is almost identical with the one of ajmaline, with the exception of small differences in the intensity of some peaks; the mass spectrum (Fig. 2) of 21-deoxyajmaline (II) differs merely in the appropriate shifts attributed to the absence of one oxygen atom, and in the M − 29 peak as discussed above; the spectrum[3] of 17-epi-21-deoxyajmaline (III) is practically identical with the former; and the spectrum[3] of tetraphyllicine (IV) is similar to the one of ajmaline except that the molecular ion occurs at m/e 308 and is of relative higher intensity, owing to the higher degree of unsaturation.
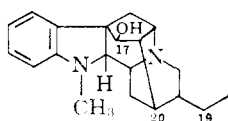

II (III = 17 epimer)
(IV = 19,20-dehydro)

In contrast to the above structural modifications which affected the mass spectrum only in a minor way, the simple conversion of the secondary alcohol grouping at C-17 to a carbonyl[6] or epimerization at C-2[4] drastically changes the fragmentation of the ring system.

The carbonyl group of the five-membered ring in ajmalidine (V)[10] can be eliminated as CO, a process that would have to involve loss of hydroxycarbene, a very unlikely species compared with CO, in the case of a 17-hydroxyl compound, and this process is thus observed with I but not with V. Cleavage of the C-2, C-3 bond leads then directly to mass 144 ($C_{10}H_{10}N$) which is relatively much more abundant in the spectrum of V than in I.

The genesis of the peak at mass 198 ($C_{13}H_{12}NO$) in the spectrum of ajmalidine (V) was discussed in more detail earlier[6] and is analogous to the one discussed above for m/e 200 in I (Fig. 1). Introduction of a methoxyl group into the benzene ring has no influence on the fragmentation process, and the mass spectrum (Fig. 3) of vomalidine (VI) corresponds to the one of V with the exception of the shift by 30 mass units (CH_2O) of all those ions retaining the methoxyl group.[6]

V
(VI = 12-methoxy)
(VII = 21-deoxy)
(VIII = 19,20-dehydro-21-deoxy)

m/e 198 ($C_{13}H_{12}NO$)
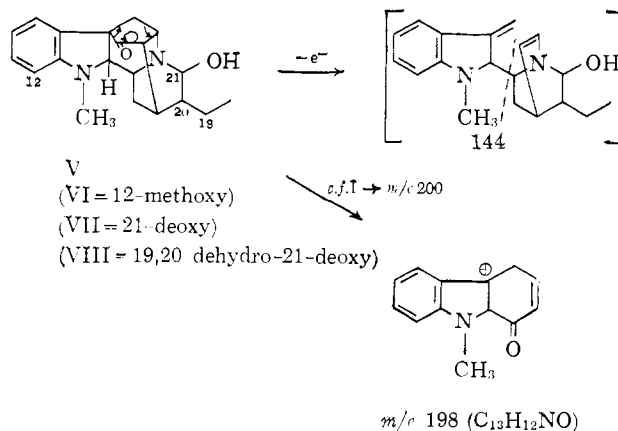
The involvement of the 21-hydroxyl group in the process leading to m/e 198 (see mechanism of forma-

(10) The spectrum of V has been reproduced previously (ref. 6). To avoid repetition, the spectrum of VI is shown in this paper (Fig. 3).
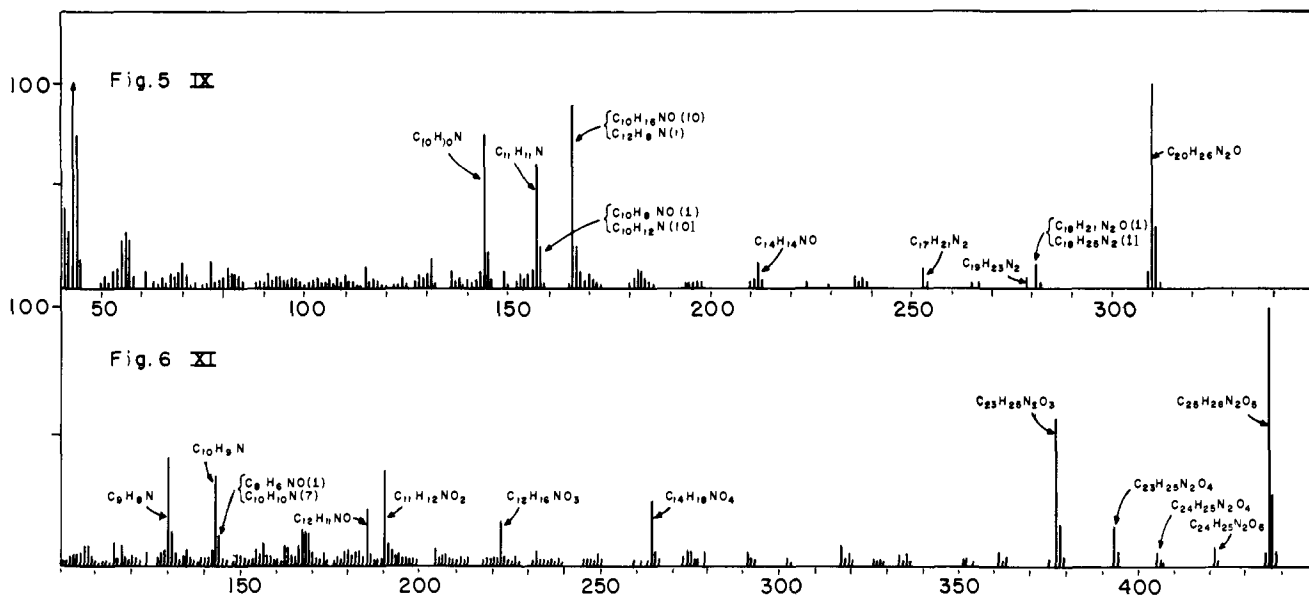
Fig. 5.—Mass spectrum of 21-deoxy-2-epiajmaline (IX).
Fig. 6.—Mass spectrum of O,N-diacetylquebrachidine (XI).

tion for m/e 200 in I) is pointed out by the mass spectrum (Fig. 4) of 21-deoxyajmalone (VII) which represents a transition between the ajmaline type and ajmalidine type inasmuch as it has a pronounced peak attributed to loss of CO as well as CHO, and a very intense peak at m/e 144 ($C_{10}H_{10}N$), while the peak at m/e 198 is much less intense than in V or m/e 228 in VI.

The spectrum (not shown) of tetraphyllisone (VIII) corresponds to the one of VII, with the exception of the shift of the molecular ion to 306, rather than to the one of ajmalidine (V) because VIII does not possess a 21-hydroxyl. The mass spectral pattern[6] typical for V and VI thus requires the presence of both the 17-keto group as well as a 21-hydroxyl.

The most drastic change in the fragmentation is, however, produced by epimerization at C-2. The mass spectrum (Fig. 5) of 21-deoxy-2-epiajmaline (IX) is completely different from the spectrum of II (Fig. 2). The peak at mass 182 and 183 are practically absent, while a new one appears at mass 166. This ion, which is the most intense one in the spectra, has an elemental composition $C_{10}H_{16}NO$, in addition to a minor component $C_{12}H_8N$. The former has a high hydrogen-to-carbon ratio and represents thus the alicyclic portion of the molecule; the following process is proposed for its formation.[11]
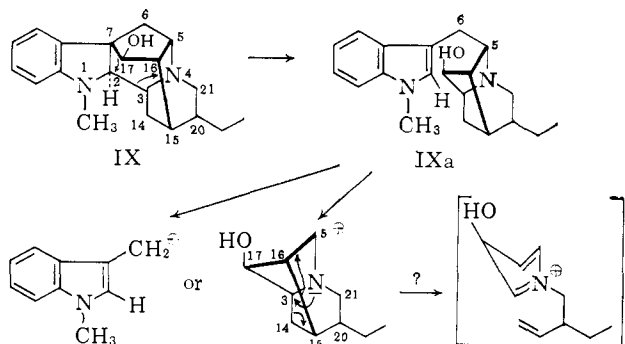

(11) The last step suggests one of the possible electron shifts through which this bridged ion can be stabilized. The one depicted is preferred on the basis of the spectra[4] of compounds lacking the N,C-21 bond.

This type of fragmentation pattern was first observed with quebrachidine (X), its diacetyl derivative XI, and vincamedine (XII)[12] in the course of the determination of the structure of X.[5] The intense peak at
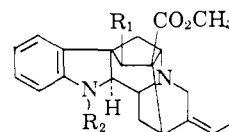
X, R_1 = OH, R_2 = H
XI, R_1 = OCOCH₃, R_2 = COCH₃
XII, R_1 = OCOCH₃, R_2 = CH₃

m/e 222 in the spectrum of X corresponds to 166 + 58 (contribution by additional carbomethoxy group) − 2 (19,20 double bond) as required for such a structure and this peak shifts to m/e 264 in the 17-acetates XI and XII (Fig. 6). The elemental composition of this peak ($C_{14}H_{18}NO_4$) is in agreement with the ion
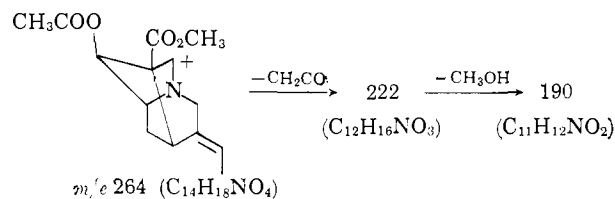
and the mass shifts in comparison with O,N-di(trideuterioacetyl)quebrachidine (XI-d_6, peaks at 191, 223, and 267)[4] also support this proposal. The shifts of the peaks at m/e 130, 144, and 185 in XI to 131, 145, and 188 in XI-d_6 corroborate the presence of an N-acetyldihydroindole system which eliminates the acetyl group as ketene.[9] Its retention gives rise to the peak at m/e 185 (188 in XI-d_6). The peaks at high mass in Fig. 6 are self-explanatory (loss of CH₃, CH₃O, CH₃CO, and CH₃COO).

The striking difference in the mass spectra as a function of the stereochemistry at C-2 is attributed to the

(12) For structure see M.-M. Janot, J. LeMen, J. Gosset, and J. Levy, Bull. soc. chim. France, 1079 (1962).

spatial arrangement of the atoms and bonds that have to be rearranged in the key step of the fragmentation of II and IX, respectively. In the ajmaline series, the hydrogen at C-2 is sufficiently close to C-17 to lead to its migration with simultaneous aromatization of the dihydroindole to an indole system (I → Ib, see above). In the 2-epi series, this hydrogen is, however, *trans* and far away from C-17, thus blocking that process. Aromatization is only possible by rearranging the C-2, C-3 bond to a C-3,C-17 as implied in the process IX → IXa. It should be noted, however, that the bonds broken and the bonds rearranged are spatially the same (around C-2) in both processes which thus are very closely related although leading to entirely different fragments. These two groups of epimers thus represent a rather unique example in which the stereochemistry at one center so completely changes the fragmentation of a carbon skeleton. The effect is here so drastic because of the very rigid arrangement of the polycyclic ring system.

Experimental

Mass Spectra.—The conventional spectra were taken with a single-focusing mass spectrometer (CEC 21-103C) equipped with a heated inlet system operated at 175°; ionizing current 10 or 50 μa., ionizing voltage 70 v.

The high-resolution spectra were obtained with a double-focusing mass spectrometer (CEC 21-110), using a photographic plate for recording. The samples were introduced directly into the ion source and perfluorokerosene was used as the mass standard; ionizing current 100 μa., ionizing voltage 70 v. All the line positions were measured and then converted to accurate masses and corresponding elemental compositions with the aid of a computer.[13] A selected group of these values is shown in Fig. 1–6.

(13) D. Desiderio and K. Biemann, 12th Annual Conference on Mass Spectrometers, Montreal, June, 1964.

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Three-Membered Rings. I. Conjugative Properties and Electronic Spectra of Arylcyclopropanes, Oxiranes, and Thiiranes[1]

BY L. A. STRAIT, ROGER KETCHAM, D. JAMBOTKAR, AND VINOD P. SHAH

The ultraviolet spectra of a series of *p*-substituted phenylcyclopropanes, styrene oxides, and styrene sulfides have been examined with regard to chromophoric enhancement as measured by the effect of the *p*-substitution on the "primary" ($^1A_{1g}$–$^1B_{1u}$) electronically forbidden transition in benzene. It is shown that, relative to benzene, oxirane and thiirane are electron withdrawing, whereas cyclopropane is electron donating. Thus *p*-methoxy substitution was observed to shift conjugatively and enhance the ultraviolet "primary" absorption bands of phenyloxirane and thiirane but had little effect on phenylcyclopropane; *p*-nitro substitution showed the reverse effect. These observations are in agreement with second-order resonance effects and clarify some of the conflicting observations and conclusions concerning the unsaturation properties of the three-membered ring systems.

The electronic spectra of molecules containing three-membered rings adjacent to unsaturated groups have provided an effective method of demonstrating the conjugative properties arising from the unsaturation character of these rings.[2] These effects in cyclopropane have been documented by a variety of physical[3] and chemical[4] techniques and have been described theoretically by Coulson[5] and Matsen[6] and their co-workers.

(1) Supported, in part, by Cancer Research Funds, University of California, and an American Cancer Society Institutional Grant 1N 33D. This work has been reported in part at the 1963 Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy and at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964. Abstracted from the Ph.D. Theses of D. Jambotkar and V. P. Shah.

(2) (a) R. A. Raphael, "Chemistry of Carbon Compounds," Vol. IIA, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1953, pp. 25–28; (b) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Inc., Englewoods Cliffs, N. J., 1963, pp. 320–326.

(3) (a) M. T. Rogers, J. Am. Chem. Soc., 69, 2544 (1947); (b) V. T. Aleksanian, Kh. E. Sterin, M. Yu. Lukiva, I. L. Saforova, and B. A. Kayonskii. Optika i Spectroskopia, 7, 114 (1959); (c) I. M. Klotz, J. Am. Chem. Soc., 66, 88 (1944).

(4) (a) R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, J. Org. Chem., 27, 733 (1962); (b) R. Fuchs and J. J. Bloomfield, ibid., 28, 1910 (1963); (c) R. R. Kostikov and I. A. Dyakonov, Dokl. Akad. Nauk S.S.S.R., 149, 853 (1963); (d) P. J. C. Fierens and J. Nasielski, Bull. soc. chim. Belges, 71, 186 (1962).

(5) (a) C. A. Coulson and W. E. Moffitt, J. Chem. Phys., 15, 151 (1947); (b) C. A. Coulson and T. H. Goodwin, J. Chem. Soc., 2851 (1962); (c) ibid., 3161 (1963).

(6) J. F. Music and F. A. Matsen, J. Am. Chem. Soc., 72, 5256 (1950).

Spectroscopic evidence of the electronic interaction of oxirane with adjacent unsaturated groups has been contributed by Rogers[3a] and more recently by Cromwell[7] and co-workers who demonstrated that both oxirane and azirane are capable of transmitting as well as extending electronic effects in variously substituted chalcone oxides and imines.[7] However, a contradictory effect was noted by Cromwell in the case of *p*-methoxy substitution on the β-phenyl ring and was not satisfactorily explained. Also the failure of the cyclopropyl ring to transmit conjugation in some systems as reported by Eastman[9] and Mariella[10] was unexplained. These apparent anomalies may on the one hand reflect the difficulty of interpretation of the perturbations of the

(7) (a) N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang, ibid., 83, 974 (1961); (b) N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, ibid., 82, 4241 (1960). Cromwell concluded that the three-membered rings, in addition to extending conjugation by overlap with the adjacent aryl carbonyl group, also could transmit the effect from an α-phenyl group through the oxirane ring to the arylcarbonyl. We have observed a similar effect in a series of substituted stilbene oxides which has been presented in a preliminary report[8] and will be presented for publication in greater detail.

(8) L. A. Strait, D. Jambotkar, R. Ketcham, and M. Hrenoff, "Intern. Conf. Spect. 9, Lyons, France, 1961," Trans. Vol. 1–3, p. 125, G. A. M. S., Paris 15°, France, 1962.

(9) (a) R. H. Eastman, J. Am. Chem. Soc., 76, 4115 (1954); (b) R. H. Eastman and J. C. Selaver, ibid., 76, 4118 (1954); (c) A. L. Goodman and R. H. Eastman, ibid., 86, 908 (1964).

(10) R. P. Mariella and R. R. Raube, J. Org. Chem., 18, 282 (1953); cf., however, R. J. Mohrbacher and N. H. Cromwell, J. Am. Chem. Soc., 79, 401 (1957), and E. M. Kosower and M. Ito, Proc. Chem. Soc., 25 (1962)