TABLE I

RELATIVE SPECIFIC ACTIVITIES OF THE ALKALOIDS AND THEIR DEGRADATION PRODUCTS[a]

Compound	Activity	Compound	Activity	Compound	Activity
Haemanthamine (I, R = H)	1.00	Haemanthidine (I, R = OH)	1.00	Tazettine (II)	1.00
Oxohaemanthamine	1.00	Tazettine (II)	1.04	Tazettine methiodide	0.97
2-Methyl-4,5-methylenedioxybiphenyl (IV)	0.00	Tazettine methiodide	1.04	6-Phenylpiperonyl alcohol (VI)	0.00
N-Tosylsarcosine (V)	1.00	6-Phenylpiperonyl alcohol (VI)	0.00	Dimethylglycine hydrochloride (VII)	0.95
Formaldehyde dimethone	0.00	Dimethylglycine hydrochloride (VII)	1.06	Carbon dioxide	0.95
Methanol 3,5-dinitrobenzoate	0.00	Formaldehyde dimethone	0.00	Formaldehyde dimethone	0.00
Carbon dioxide	0.9[b]	Carbon dioxide	1.00	N,N-Dimethyl-*p*-toluenesulfonamide	0.00
		N,N-Dimethyl-*p*-toluenesulfonamide	0.00		

[a] Samples were counted in a Packard Tri-Carb Scintillation Counter in toluene or dioxane-napthalene scintillator solutions. The carbon dioxide was collected directly from the Kolbe reaction in hyamine hydroxide 10-X and counted in toluene. [b] Based on obtaining 78% of the counts compared to a model run which yielded 87%.

Degradation of haemanthamine (I, R = H) by methods outlined earlier[3] has revealed that *all* the radioactivity in this alkaloid resides at C_{11}. The degradation product, 2-methyl-4,5-methylenedioxybiphenyl (IV), which represents rings A, C, and the benzylic carbon, is totally inactive. To corroborate this finding, radioactive haemanthidine (I, R = OH) was converted to tazettine[6] and then degraded by the Hofmann method[7] to 6-phenylpiperonyl alcohol (VI) and dimethylglycine hydrochloride (VII). The same degradation was applied to the radioactive tazettine isolated from the plants. In both cases, the 6-phenylpiperonyl alcohol was completely inactive. Kolbe electrolysis[3] of the dimethylglycine hydrochloride provided radioactive carbon dioxide and inactive formaldehyde isolated as the dimethone derivative,[3] indicating that 3-C^{14}-tyrosine or a close biological equivalent can serve as a precursor of ring C and the two-carbon chain of ring D with no scrambling of the label.[8] Table I lists relative activities of the degradation products of these alkaloids.

These data show that either a C_6-C_1 unit is not the precursor of ring A and the benzylic carbon atom of haemanthamine, haemanthidine, and tazettine, or that, if such a unit is the precursor, it cannot be derived from tyrosine in *S. formosissima*. This is in contrast to the results of Suhadolnik and Fischer[9] who showed that 3-C^{14}-phenylalanine is a precursor of ring A and the benzylic carbon of lycorine (III, R = H; OH at C_2). Further work will be required to establish whether these results are a reflection of different biosynthetic pathways for 5,10b-ethanophenanthridine alkaloids and those of the lycorine type. However, there have been recent indications of some differences in that the aromatic substitution pattern[10] of falcatine (III, R = OCH_3) is as expected from biogenetic theory[11] whereas that of the powellane alkaloids[12] requires a rearrangement step. The biosynthetic inter-relationships of alkaloids in this series are being further studied.

Acknowledgment.—We are grateful to Dr. R. Binks for help with the extraction work and to Dr. P. W. Jeffs for kindly informing us of his incorporation of 3-C^{14}-tyrosine into haemanthamine (without scrambling).

(6) For one method of conversion of haemanthidine to tazettine, see H.-G. Boit and W. Stender, *Chem. Ber.*, **89**, 161 (1956).

(7) *Cf.* W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 2962 (1955).

(8) Strictly, these results prove that ring C and the asterisked carbon of ring D can be derived from tyrosine. However, our earlier work[3] established incorporation of the carbon atoms from position 2 of tyrosine into position 12 of haemanthamine. That the C_6-C_1 unit is incorporated intact in all three alkaloids is supported by the isolation of radioactive haemanthamine, haemanthidine, and tazettine from *S. formosissima* fed with 2-C^{14} tyrosine.

(9) R. J. Suhadolnik and A. G. Fischer, Abstracts, American Chemical Society, Chicago, Ill., 1961, p. 39Q; see also *Chem. Eng. News*, **39**, 51 (1961).

(10) K. Torssell, *Acta. Chem. Scand.*, **15**, 947 (1961).

(11) D. H. R. Barton and T. Cohen, "Festschrift Arthur Stoll," Birkhäuser, Basel, 1957, p. 117.

(12) H. A. Lloyd, E. A. Kielar, R. J. Highet, S. Uyeo, H. M. Fales and W. C. Wildman, *Tetrahedron Letters*, 105 (1961).

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STEREOCHEMICAL REQUIREMENTS OF MULTIPLE REARRANGEMENTS. EVIDENCE FOR CLASSICAL CARBONIUM ION INTERMEDIATES

Sir:

Although the importance of non-classical, mesomeric carbonium ions as intermediates in Wagner–Meerwein rearrangements has been stressed in recent years, the mechanistic role played by the classical, non-mesomeric species has not been made clear. We report here some experimental evidence that implies the presence of *both* classical and non-classical ions in a case of multiple rearrangement.

Nitrous acid deamination of *endo*-2-aminomethylnorbornane I previously[1,2] had been shown to give mostly *endo*-(*equatorial*)-bicyclo[3.2.1]octanol-2 II and a little of the *exo*-(*axial*)-isomer III. Using

(1) K. Alder and R. Reubke, *Chem. Ber.*, **91**, 1525 (1958).

(2) A. A. Youssef, M. E. Baum and H. M. Walborsky, *J. Am. Chem. Soc.*, **81**, 4709 (1959).

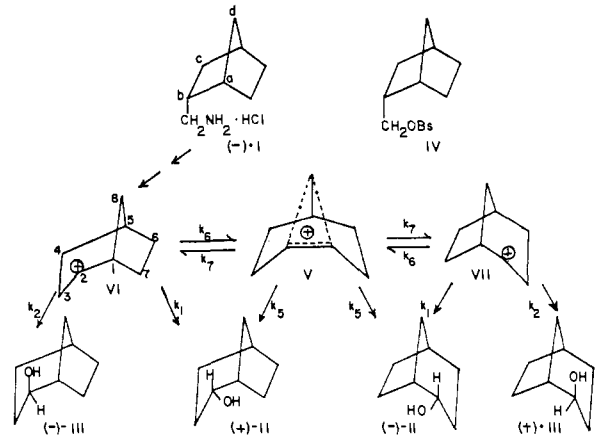
vapor chromatography as an analytical tool and optically active starting material[3] as a mechanistic probe, we have re-studied this deamination as well as the acetolysis of the related racemic *p*-bromobenzenesulfonate IV.

From I in aqueous acetic acid–sodium nitrite there are obtained 90–92% of II and 8–10% of III, and from IV in acetic acid–sodium acetate, 90–92% of the acetate of II and 8–10% of the acetate of III. Optically active I, 52.4% optically pure,[3] gives on deamination *optically active* II, $[\alpha]_D$ +0.858° ($CHCl_3$), +0.684° (ethanol), and *optically active* III, $[\alpha]_D$ −3.67° (ethanol), both isolated by repeated cycles of vapor chromatography. Intervention of the symmetrical mesomeric cation V[4] as the sole intermediate is thus excluded, since purely racemic products then would have resulted.

Nevertheless, both II and III are partially racemized: From the highest rotation reported[5] for II, the minimum value for 52.4% optically pure II can be calculated to be 4.25° ($CHCl_3$); the I → II reaction therefore involves at least 80% racemization. From data reported elsewhere,[6] a minimum value for 52.4% optically pure III can be calculated to be 6.76° (ethanol); the I → III reaction therefore involves at least 46% racemization.

From the observation that Oppenauer oxidation of II of $[\alpha]_D$ +0.684° (ethanol) gives bicyclo[3.2.1]octanone-2 of $[\alpha]_D$ +5.34° (ethanol), while III of $[\alpha]_D$ +5.25° (ethanol) gives the same ketone with $[\alpha]_D$ −50.3°, we conclude that the ratio of rotations II/III when both alcohols are of identical optical purity is 1.23. The ratio of rotations II/III when both are formed from I is 0.186. Therefore, the extents of racemization of II and III formed from I differ, and II is more highly racemized than III.

These results are not compatible with a mechanism involving the enantiomeric classical cations VI and VII as the sole intermediates either, since the optical purities of II and III would then be identical. The data require that there be at least two different product-forming intermediates and that the ratios of products II and III from each be different. The simplest scheme accommodating these requirements is shown in the adjacent diagram. That this mechanism fits the results may be deduced by inspection and also by a steady-state analysis, which shows that the kinetically controlled product ratio is given by eq. 1. When $k_5 = 0$, *i.e.*, when V is not a product-forming intermediate, the ratio becomes unity; when $k_5 > 0$, the only condition for the ratio to be less than unity, as is observed experimentally, is a trivial one, namely,



that $(k_5/k_7) + 1 > k_6/(k_6+k_1+k_2)$, which is necessarily true.

$$\frac{[(+)\text{-II}]}{[(-)\text{-II}]} \Big/ \frac{[(-)\text{-III}]}{[(+)\text{-III}]} = \frac{k_7}{k_1k_7 + k_5(k_6 + k_1 + k_2)} \times \left[k_1 + \frac{k_5k_6(k_6 + k_1 + k_2)}{(2k_7 + 2k_5)(k_6 + k_1 + k_2) - k_6k_7}\right] \quad (1)$$

Classical cation VI apparently is diverted to mesomeric cations and to products substantially faster than it is transformed into its conformational isomer VIII, since a characteristic product from VIII,[6] bicyclo[2.2.2]octanol-2, constitutes at most 1–2% of the product from I.

Conversion of VI to V rather than to the isomeric non-classical ion IX is expected as a consequence of conformational factors, which place the axis of the *p*-orbital at C.2 in VI nearly parallel to the C.1-C.8 bond axis and nearly orthogonal to the C.1-C.7 bond axis (*cf.* VIa).

In principle, the role assigned in the scheme to non-classical ion V can be assumed by another hypothetical non-classical ion in which C.2 and C.4 are bridged by hydrogen. Experiments now in progress are expected to reveal whether such species are involved. In any case, whatever the nature of the non-classical intermediates, they are either not identical with or are partitioned in a different manner from those responsible for the exclusive formation of II[4a] in other circumstances.

Although optically active non-classical intermediates X and its mirror image may be imagined as alternatives to classical ions VI and VII, direct conversion of X to III would require that the mesomeric bridge be opened with retention of configuration. Such an assumption, while perhaps not rigorously excluded, at least has no precedent and appears to us unnecessarily drastic. We therefore prefer the formulation in terms of VI and VII. (There are no grounds at present for eliminating X as a possible intermediate between I and VI.)

The stepwise nature of the multiple rearrangement observed here probably arises from the geometry of I, which makes it stereoelectronically unfavorable for the migration of c from b to the CH_2 side-chain to occur in concert with the movement of d from a to a position between a and b. In this respect, the situation is formally analogous to that in the solvolyses[7] of *endo*-norbornyl arene-

(3) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).

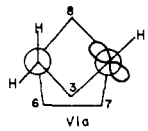
(4) Previously postulated as an intermediate (a) in the acetolysis of II (OTs instead of OH), which gives exclusively II acetate [H. L. Goering and M. F. Sloan, *ibid.*, **83**, 1397 (1961)], and (b) in the acetolysis of 4-cycloheptenylcarbinyl *p*-bromobenzenesulfonate, which gives predominantly II acetate [G. Le Ny, *Compt. rend.*, **251**, 1526 (1960)].

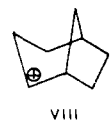
(5) H. M. Walborsky, M. E. Baum and A. A. Youssef, *J. Am. Chem. Soc.*, **83**, 988 (1961).

(6) J. A. Berson and D. Willner, *ibid.*, **84**, 675 (1962).

(7) S. Winstein and D. Trifan, *ibid.*, **74**, 1147 (1952).

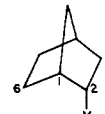
sulfonates XI, which pass through a classical intermediate before proceeding to a mesomeric cation. The relative geometry of c and d in I is roughly the same as that of Y and C.6 in XI.


VIa


VIII


IX


X


XI

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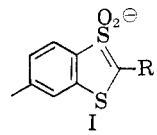
STUDIES ON d-ORBITAL CONJUGATION. II. LACK OF AROMATICITY IN SYSTEMS CONTAINING A CARBANION-SULFONE DOUBLE BOND[1]

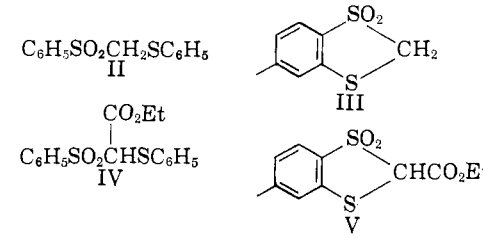
Sir:

With the developing evidence[2] that the sulfone group, and other systems with strongly electronegative second row elements, can interact with adjacent unsaturated centers by a conjugation mechanism, it has become increasingly common to write structures such as I, with a double bond which (probably) involves the use of a 3-d orbital by sulfur. Among the properties of such a double bond which are of interest, its stereochemistry and its ability to conjugate seem fundamental. It has been suggested[3] that double bonds of this type can form aromatic systems if they are cyclically conjugated, but a counter view has been advanced by Dewar,[4] who suggests that the stereoelectronic properties of d-orbitals will cause pi electron nodes in the cyclic system, so that aromatic stabilization will not be observed.


I

Several compounds are already known which are of interest in this connection. The cyclic phosphonitrilic halides have been suggested to be aromatic,[3] and Price has reported a derivative of "thiabenzene"[5] in which 10-electron sulfur is part of the cyclic system. However, no evidence for aromatic stabilization of these systems because of any special effect resulting from their cyclic conjugation is available, and the situation is also ambiguous for two known benzothiepin dioxides[6] which are d-orbital analogs of tropone.

In order to obtain evidence on this question we have examined the acidity of compounds II–V. The carbanions derived from III and V will have contributions from resonance forms of the type I, and if such a system is strongly stabilized by cyclic conjugation, as is the analogous aromatic benzothiazole system, then this should be reflected in an increased acidity of III and V. The choice of II and IV as open-chain analogs is justified by our finding[1] that the disulfones related to II–V have comparable acidities; this with the other previously reported comparisons[1] indicates that no special steric effect invalidates the comparison between II, IV and III, V.


II III IV V

The sulfide sulfone (II), m.p. 55–57°,[7] was prepared by oxidation of methylene diphenyl disulfide with hydrogen peroxide in acetic acid to the corresponding sulfoxide sulfone, m.p. 67–68°,[7] and reduction of the latter to II with zinc/acetic acid. 6-Methyl-1,3-benzodithiolane 3,3-dioxide (III), m.p. 108–110°,[7] was prepared by a similar sequence. Oxidation of the benzodithiolane yielded a mixture of the two possible sulfoxide sulfones, and reduction yielded both III and the isomer, 5-methyl-1,3-benzodithiolane 3,3-dioxide, m.p. 67–69°.[7] The assignment of respective structures to these isomers was based on n.m.r. spectral studies on the aromatic hydrogens, and will be described in the full publication.

When II was allowed to stand for several hours with dimethoxyethane/D_2O/triethylamine, the recovered starting material was completely deuterated in the methylene group, as evidenced by its n.m.r. spectrum, and III was similarly converted to the 2,2-dideuterio derivative. Treatment of this deuterated II with one mole of butyllithium in ether, addition of dimethoxyethane to effect complete solution, and addition of this solution to 2*N* HCl afforded recovered II with one proton in the methylene group, appearing at 5.74 τ in the n.m.r. Deuterated III was similarly converted to the monoanion by butyllithium, as revealed by the appearance, after processing as above, of one proton at 5.76 τ. When the anion of deuterated III was prepared first, and an equimolar amount of deuterio-II then was added, the resulting homogeneous solution, after quenching, gave a mixture of II and III which was analyzed by the use of n.m.r. A

(1) For Part I, *cf.* R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.*, **83**, 4100 (1961).

(2) For a review, see G. Cilento, *Chem. Rev.*, **60**, 147 (1960).

(3) D. P. Craig, *J. Chem. Soc.*, 997 (1959).

(4) M. J. S. Dewar, F. A. C. Luchen, and M. A. Whitehead, *ibid.*, 2423 (1960); *cf.* however M. J. S. Dewar and V. P. Kubba, *J. Am. Chem. Soc.*, **82**, 5685 (1960).

(5) G. Suld and C. C. Price, *ibid.*, **83**, 1770 (1961).

(6) W. Truce and F. Lotspeich, *ibid.*, **78**, 848 (1956); V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

(7) These compounds gave C and H analyses within 0.3% of theoretical and their infrared and n.m.r. spectra were consistent with the assigned structures.