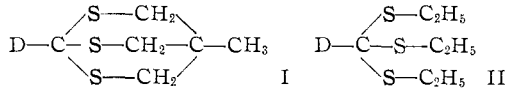
DEUTERIUM–HYDROGEN EXCHANGE REACTIONS OF BRIDGEHEAD α-DEUTERIUM IN BICYCLIC TRISULFIDE

Sir:

During studies of the base-catalyzed deuterium–hydrogen exchange reactions of organic sulfide compounds and of the corresponding oxygen analogs, we have found that the exchange rate of 1-deuterio-4-methyl-2,6,7-trithiabicyclo[2,2,2]octane (I) is appreciably higher than that of deuteriated ethyl orthothioformate (II).



I II

Table I lists kinetic data for a few representative compounds during *tert*-butoxide and ethoxide catalyzed exchange reactions. All the compounds listed, I, II, deuteriated ethyl thioethylal (III), 1-deuterio-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (IV) and deuteriated ethyl orthoformate (V), were synthesized by known methods except for the starting deuteriated ethyl orthoformate (V) which was prepared by the alcoholysis of deuteriated formiminoether hydrochloride. The deuterium content in all these compounds (greater than 90%) was determined by n.m.r. analyses and the deuterium–hydrogen exchange kinetics were followed by infrared analyses. As shown in Table I, no exchange reactions of oxygen compounds were observed under the conditions listed. It has been suggested that the α-hydrogen of diethyl mercaptal is displaced under strongly alkaline conditions,[1] and we have confirmed this. The substitution of one additional ethylmercapto group at the α-carbon of the mercaptal increases the reactivity by more than ten thousand fold, which corresponds to a difference in free energy of activation of about 7.8 kcal. mole^{-1}. This means that 3d-orbital resonance is the major contributing factor in the facile deuterium–hydrogen exchange reaction of the sulfur compounds, while the electron-withdrawing inductive effect contributes little. Since earlier work indicates that there is no strict angular requirement for d–p overlap of the C–S[2] π-bond as there is for p–p overlap, one would expect the rate of exchange of I to be of the same order of magnitude as that of II or possibly somewhat lower than that of II because of its less favored solvation. However, we have found that the rate of I was about three powers of ten larger than that of II in ethanol at 50°, corresponding to a difference in free energy of activation of about 4.6 kcal. mole^{-1}. This seems rather strange when one recalls the well-known work by Doering and Levy[3] that the bicyclic trisulfone was less acidic than the acyclic trisulfone.

The large rate difference between I and II seems likely to be caused by two main factors which would operate jointly. One factor is that an effective 2p–3d overlap could be attained by constraining

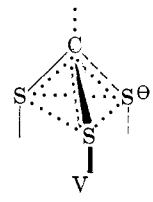
TABLE I

KINETICS FOR THE BASE-CATALYZED DEUTERIUM-HYDROGEN EXCHANGE REACTIONS

Cpd.	Base	Solvent	Temp., °C.	First order reaction rate constant, $k_1 \times 10^4$ sec.$^{-1}$[a]
I	EtONa[b]	EtOH	50	4.52
II	EtONa	EtOH	50	0.00375[c]
II	EtONa[b]	EtOH	80	0.174
II	EtONa[b]	EtOH	90	0.582
II	EtONa[b]	EtOH	100	1.59
II	*t*-BuOK[d]	*t*-BuOH	40	0.62
II	*t*-BuOK[d]	*t*-BuOH	50	1.55
II	*t*-BuOK[d]	*t*-BuOH	60	3.64
II	*t*-BuOK	*t*-BuOH	138	699.5[e]
III	*t*-BuOK[d]	*t*-BuOH	138	0.0473
I	*t*-BuOK[d]	*t*-BuOH	50	Very fast
IV	*t*-BuOK[d]	*t*-BuOH	138	No exchange (in 5 hr.)
V	*t*-BuOK[d]	*t*-BuOH	112	No exchange (in 20 hr.)

[a] From measurement at 862 cm.$^{-1}$ and 713 cm.$^{-1}$ for I, 1150 cm.$^{-1}$ and 872 cm.$^{-1}$ for II, 1177 cm.$^{-1}$ and 890 cm.$^{-1}$ for III, 3030 cm.$^{-1}$ and 2280 cm.$^{-1}$ for IV, and 1730 cm.$^{-1}$ and 1693 cm.$^{-1}$ for V. [b] 0.107 *M*. [c] Extrapolated value. [d] 0.097 *M*. [e] Extrapolated value.

sulfur atoms at some fixed positions as in I. This may be related to the facts that the resonance energy of 1,4-dithiadiene (15–30 kcal. mole^{-1})[4] is very large and that the resonance energy of thiophene (31 kcal. mole^{-1})[5] is greater than that of furan (23 kcal. mole^{-1}).[5] The second is that the three sulfur atoms of I are closely packed together in a ring system and each sulfur atom has lone electron pairs that could be used for 3p–3d overlapping between three sulfur atoms. There are many u.v. data on alkyl mercaptals, alkyl and benzyl sulfides that suggest such interaction.[6] Therefore the structure (V) seems a likely representation of the intermediate anion of I in this exchange reaction. The sulfones, having no unbonded 3p-orbitals, are incapable of forming a similar interaction. One supporting evidence for this consideration may be the ultraviolet spectra of I, II and of



V

III shown in Table II. The absorption maximum of the ring compound, I, is shifted toward substantially longer wave lengths compared to that of the acyclic compounds and the whole spectrum of I is somewhat different from those of II and III, while the extinction coefficient of I is greater than those of the other two. These indicate that I has a different chromophore. Presumably, a structure similar to V would contribute in the photo-

(1) J. F. Arens, M. Fröling and A. Fröling, *Rec. trav. chim.*, **78**, 663 (1959).

(2) (a) G. E. Kimball, *J. Chem. Phys.*, **8**, 188 (1940); (b) D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel and L. E. Sutton, *J. Chem. Soc.*, 332 (1954); (c) C. C. Price and S. Oae, forthcoming book. "Sulfur Bonding," Ronald Press, New York, N. Y.

(3) W. E. Doering and L. K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955).

(4) W. E. Parham, 15th A.C.S. Organic Chem. Symposium, June 20, 1957, Rochester, N. Y.

(5) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, pp. 197.

(6) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949); H. P. Koch, *J. Chem. Soc.*, 387 (1949); see details in ref. 2c.

excited state of I. We expect that a study on the proton dissociation of the corresponding trisulfoxides and trisulfonium compounds will shed further light on the nature of the unusual reactivity of this bicyclic compound.

TABLE II

ULTRAVIOLET SPECTRA OF SULFIDES IN DIOXANE[a]

Compound	λ_{max}, mμ	log ε
I	248	3.1
II	236	3.0
III	236	2.8

[a] These spectra were the same in ethanol solution containing 0.1 *M* of sodium ethoxide.

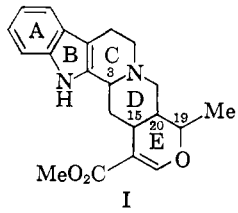
DEPARTMENT OF CHEMISTRY SHIGERU OAE
RADIATION CENTER OF OSAKA PREFECTURE
SAKAI, OSAKA, JAPAN WAICHIRO TAGAKI
ATSUYOSHI OHNO

RECEIVED OCTOBER 10, 1961

THE STEREOCHEMISTRY OF AJMALICINE AND TETRAHYDROALSTONINE[1]

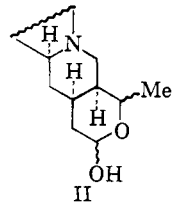
Sir:

While the relative configuration of C(3)-H and C(15)-H in the alkaloids (I) ajmalicine and tetrahydroalstonine has been shown to be *cis*[2] and their absolute configuration in ajmalicine to be α,[3] the stereochemistry of C(19) of neither alkaloid is known and that of C(20) is based on nonclassical, as yet untested, investigations.[2,4] We now wish to report data from degradation and proton magnetic resonance studies which revise previous structure assignments and establish the complete stereochemistry of ajmalicine and related alkaloids.

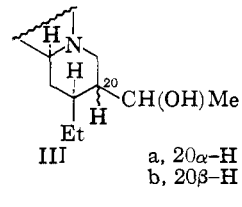


I

Alcoholic alkali and short aqueous acid treatments[3] of tetrahydroalstonine (I) yielded tetrahydroalstonial (II), m.p. 173–177°, 210–214° (Found: N, 8.83)[5] which on Wolff–Kishner reduction afforded 19-corynantheidol (IIIa); picrate, m.p. 216–222° (Found: C, 57.07; H, 5.62; N, 13.63). Oppenauer oxidation of the latter gave 19-corynantheidone (IVa), m.p. 152–153° (Found: C, 77.17; H, 8.27; N, 9.41), which was converted to 18,19-dihydro-19-corynantheone (IVb)[3], m.p., m.m.p. 225–228°, on sodium methoxide treatment. Sodium borohydride reduction of IVb yielded ajmaliciol (IIIb),[3] m.p., m.m.p. 198–200°, and 19-isoajmaliciol, m.p. 195–197° (Found: C, 76.02; H, 8.82; N, 9.16). These facts prove ajmalicine to be a D/E *trans* and tetrahydroalstonine a D/E *cis* system. Furthermore, the latter represents one more alkaloid belonging to the biosynthetically related α C(15)-H indole alkaloid family.[3]

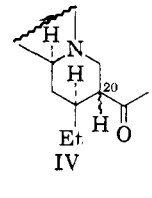


II



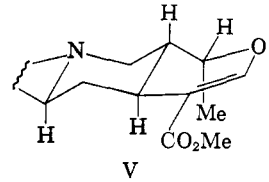
III

a, 20α–H
b, 20β–H

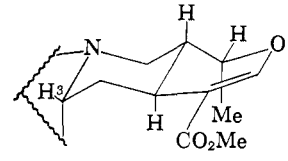


IV

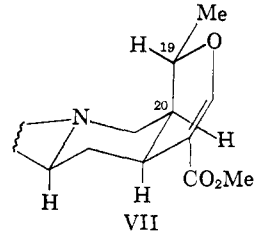
Raney nickel-induced hydrogenation of 3,4,5,6-tetradehydroakuammigine[2] to tetrahydroalstonine at high pH confirmed the previous claim[2] that akuammigine is 3-isotetrahydroalstonine. Hence the four possible stereochemical forms of the backbone of ring E heterocyclic indole alkaloids are now represented as: *normal*-ajmalicine (V); *pseudo*-3-isoajmalicine (VI)[2]; *allo*-tetrahydroalstonine (VII) and *epiallo*-akuammigine (VIII). These structural assignments are corroborated by p.m.r. spectral findings. 3-Isoajmalicine (VI), the only equatorial C(3)-H isomer, is also the only one of the compounds to exhibit a one-proton downfield signal (δ = 4.45).[6] In view of the conformational difference of the C(19) substituents in the D/E *cis* isomer pair as contrasted to the D/E *trans* pair the spin-spin coupling constants associated with the interaction of C(19)-H and C(20)-H would be expected to vary in the first set of isomers but stay constant in the second set. Indeed, inspection of the one-proton downfield octet (δ = 4.36–4.44), characteristic of C(19)-H coupling with C(20)-H and the methyl group, revealed J_{HH} to be 10.3 and 5.8 c.p.s. for VII and VIII, respectively, while 2.7 and 1.8 c.p.s. for V and VI. Tetrahydroalstonine's large J_{HH} value establishes a 19,20-*trans* diaxial configuration[7] for this alkaloid (VII) thus implying also a 19,20-*trans* arrangement for akuammigine (VIII). However, the consistently low values of the



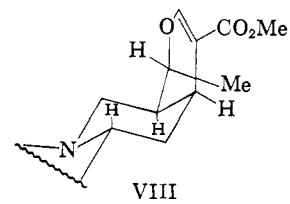
V



VI



VII



VIII

(1) This work was supported by a research grant (M-1301) from the National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare.

(2) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958), and references contained therein.

(3) E. Wenkert and N. V. Bringi, *ibid.*, **81**, 1474, 6553 (1959).

(4) N. Neuss and H. E. Boaz, *J. Org. Chem.*, **22**, 1001 (1957).

(5) This substance, m.p. 177°, was produced first by Harley-Mason and Waterfield (unpublished observation). We are indebted to Dr. Harley-Mason for this information and for a generous supply of alstonine and tetrahydroalstonial (II).

(6) Such equatorial C(3)-H systems as pseudoyohimbine, as contrasted to yohimbine (unpublished observations of this Laboratory), and some D/E *cis* Rauwolfia alkaloid derivatives (private communication from Dr. W. E. Rosen) show a similar signal.

(7) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.