

phan residues, it is compelling to consider these two phenomena may be related. In this connection Hayashi, *et al.*,¹² have shown that a tryptophan residue is involved in the formation of the enzyme-substrate complex between lysozyme and poly-N-acetylglucosamine (glycol chitin). Further, it has been reported by Hartdegen and Rupley¹³ that an inactive derivative, altered only in a single tryptophan residue, may be obtained by oxidation of lysozyme by iodine in acidic solution. This modification and loss of activity were prevented by the presence of N-acetylglucosamine.

Further improvement in instrumentation will be necessary before more accurate measurements of the small aromatic Cotton effects can be obtained. Efforts in this direction are now being made and further results will be published in due course.

(12) K. Hayashi, T. Imoto, and M. Funatsu, *J. Biochem. (Tokyo)*, **54**, 381 (1963).

(13) F. J. Hartdegen and J. A. Rupley, *Biochim. Biophys. Acta*, **92**, 625 (1964).

Alexander N. Glazer

Department of Biological Chemistry, Center for the Health Sciences
University of California, Los Angeles, California 90024

Norman S. Simmons

Department of Biophysics and Nuclear Medicine
Laboratory of Nuclear Medicine and Radiation Biology
Center for the Health Sciences, University of California
Los Angeles, California 90024

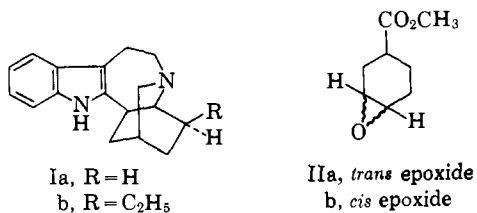
Received March 25, 1965

The Synthesis of Desethylibogamine

Sir:

We wish to report the synthesis of desethylibogamine (Ia), the first totally synthetic compound containing the carbon skeleton of the iboga alkaloids of which ibogamine (Ib) is a typical example.¹

Oxidation of methyl 3-cyclohexene-1-carboxylate with *m*-chloroperbenzoic acid gives a mixture of the *trans* and *cis* epoxides (IIa and IIb,² b.p. 60–62° (0.1



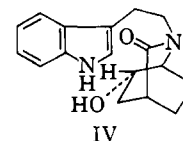
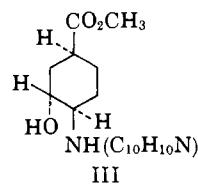
mm.)).³ Reaction of this mixture of epoxy esters with tryptamine in refluxing ethanol gave a mixture of amino alcohols⁴ which was, without separation, heated at 190 to 200° to effect cyclization of III to the N-indolyethyl-isoquinuclidone (IV). Under these conditions, the amino alcohol from the *cis* epoxide would give either a

(1) J. P. Kutney, R. T. Brown, and E. Piers, *J. Am. Chem. Soc.*, **86**, 2287 (1964), have obtained a compound containing the ibogamine ring system from the mercuric acetate oxidation of carbomethoxydihydrocleavamine.

(2) Vapor phase chromatography of this mixture indicates that there is a predominance of one isomer (probably IIa), but the degree of separation was insufficient to permit a quantitative evaluation of the relative amounts of each isomer. H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959), report that the oxidation of methyl 3-cyclohexene-1-carboxylate with perbenzoic acid gives exclusively the *trans* epoxide (IIa).

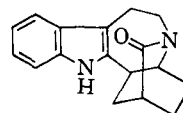
(3) Satisfactory analytical data were obtained for all new compounds reported, and all compounds were characterized by infrared and nuclear magnetic resonance spectroscopy.

(4) The infrared spectrum of this mixture indicates that a negligible amount of conversion to the amide was obtained.



δ -lactone and/or polymeric amide, and to separate the isoquinuclidone from these undesired compounds the crude mixture was heated with 5% methanolic sodium hydroxide⁵ to give IV (m.p. 178–179°, $\lambda_{\text{max}}^{\text{KBr}}$ 6.05 μ) in an over-all yield of 68%. The tosylate of this isoquinuclidone (m.p. 149–150°, 84% yield)⁶ on treatment with aluminum chloride or aluminum bromide in toluene affords desethylibogamine lactam (V, m.p. 313–315°, $\lambda_{\text{max}}^{\text{KBr}}$ 6.10 μ) in 38% yield. This compound gives a negative Ehrlich test, has a typical indole ultraviolet spectrum (λ_{max} 225, 283, and 291 m μ), and the n.m.r. spectrum is similar to that of ibogaine lactam.⁵ The attempted use of a variety of other acids to effect this cyclization led to either gross decomposition or gave recovered starting material.

Reduction of desethylibogamine lactam with lithium aluminum hydride gives desethylibogamine (I, m.p. 186–187°, λ_{max} 226, 283, and 290 m μ) in 85% yield. The n.m.r. spectrum of this compound shows a series of peaks equal to approximately eight protons in the region from τ 6.6 to 7.2. Ibogamine and ibogaine both show a series of peaks in this general region which may be assigned to the protons adjacent to the indole and the tertiary nitrogen.



In addition to providing a synthetic pathway to the iboga alkaloid ring system in relatively few steps, this work constitutes a new isoquinuclidine synthesis which has been used to prepare the unsubstituted and N-benzyl analogs of V.⁷

Acknowledgments. This work was supported by Grant NB-04589 of the National Institute of Neurological Diseases and Blindness. We wish to thank Dr. Neville Finch of Ciba Pharmaceutical Company for samples of ibogamine and N-benzylisoquinuclidone which were used as spectral references.

(5) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958), have pointed out the resistance of ibogaine lactam to basic hydrolysis.

(6) A second compound, C₂₁H₃₂N₂O₆, m.p. 245–246°, is obtained if a large excess of tosyl chloride is used. The nature of this compound will be discussed in the full paper.

(7) J. W. Huffman, C. B. S. Rao, and T. Kamiya, unpublished work.

J. W. Huffman, C. B. S. Rao, T. Kamiya

Department of Chemistry and Geology
Clemson University, Clemson, South Carolina 29361

Received February 25, 1965

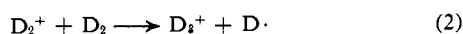
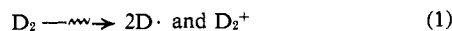
Chemical Evidence for the Occurrence and Temperature Independence of Ion-Molecule Reactions at Atmospheric Pressures

Sir:

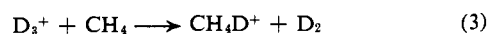
Abundant physical evidence for the occurrence of ion-molecule reactions in mass spectrometers has been

obtained.¹ However, direct chemical evidence for these reactions at high pressures has been limited.²⁻⁴ We wish to report (1) conclusive chemical evidence for the occurrence of an ion-molecule chain reaction sequence at pressures ranging from 0.85 to 0.95 atm. in the tritium β -ray-induced exchange between CH_4 and D_2 , and (2) experimental results which indicate that these reactions require no thermal activation energy.

The radiation-induced exchange between hydrogen and methane has been the object of several studies.⁵⁻⁷ Recent investigations^{4,8} indicate that ionic reactions should be expected to play an important role. In a system composed of 98.5 mole % D_2/TD (100:1) and 1.5% CH_4 , the most important intermediates are D atoms and D_3^+ ions⁸ formed *via*



It has been shown that D_3^+ reacts with CH_4 ⁸ *via*



It has been reported⁶ that CH_3D is the only organic product observed initially at 25° and that the apparent activation energy for its formation in the vicinity of 25° is 2.0 ± 0.2 kcal./mole. Both observations have been substantiated in this laboratory, and we have found $G(\text{CH}_3\text{D})$ to be 4.2 ± 0.2 molecules/100 e.v. at 25° at 1.7×10^{16} ev./cc. hr. with an initial CH_4 concentration of 3.18×10^{17} molecules/cc. From these and other considerations it has been established that atomic reactions are not solely responsible for exchange at 25°,⁶ and postulated⁶ that the CH_3D^+ ion reacts *via*



If reaction 4 occurs, the CH_5^+ ion should react further with isotopically substituted methane. Thus, addition of small quantities of CD_4 provides a test for the occurrence of reaction 4. Figure 1 shows results obtained in a reaction mixture of 98.5% D_2/TD (100:1) and 1.5% CH_4/CD_4 (23:1) at 25°. Four significant conclusions are apparent: (1) the initial rate of formation of CH_3D ($G \approx 10^2$) is indicative of a chain reaction—the rate decreases steadily and upon depletion of CD_4 attains a terminal value equal to the normal rate in the absence of more heavily deuterated methanes; (2) CD_4 disappears rapidly; (3) CHD_3 and CH_2D_2 , which are not formed initially in the absence of CD_4 , exhibit rapid growth rates, followed by their consecutive disappearance; (4) all D atoms introduced in the form CD_4 are accounted for as CH_3D and CH_2D_2 at the point at which CD_4 disappears completely. The simplest and apparently the only consistent basis for explaining these observations is the following proton and deuteron transfer chain mechanism.

(1) D. P. Stevenson and D. O. Schissler, "Chemical and Biological Action of Radiations," Vol. V, M. Haissinsky, Ed., Academic Press Inc., New York, N. Y., 1961, pp. 170-270.

(2) O. A. Schaeffer and S. O. Thompson, *J. Am. Chem. Soc.*, **80**, 553 (1958); *Radiation Res.*, **10**, 671 (1959).

(3) P. Ausloos, S. G. Lias, and R. Gorden, Jr., *J. Chem. Phys.*, **39**, 3341 (1963).

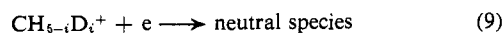
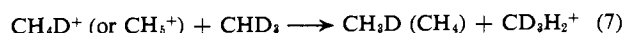
(4) P. Ausloos and S. G. Lias, *ibid.*, **40**, 3599 (1964).

(5) T. H. Pratt and R. Wolfgang, *J. Am. Chem. Soc.*, **83**, 10 (1961).

(6) R. F. Firestone, C. F. Lemr, and G. J. Trudel, *ibid.*, **84**, 2279 (1962).

(7) A. Maschke and F. W. Lampe, *ibid.*, **86**, 569 (1964).

(8) M. S. B. Munson, F. H. Field, and J. L. Franklin, *ibid.*, **85**, 3584 (1963).



The disappearance of CD_4 follows a linear first-order plot and yields a pseudo-first-order rate constant $k' = k_5(\text{CH}_{5-i}\text{D}_i^+) = 4.40 \times 10^{-4}$ sec.⁻¹, and with $[\text{CD}_4]_0$ we find the initial $G(-\text{CD}_4) = 132$ molecules/100 e.v. The magnitude of $G(\text{CH}_3\text{D})$ in the absence of CD_4 indicates that the rate of neutralization of D_3^+ is negligible. Thus, from a steady-state treatment of the above mechanism, we find $k_5/k_9^{1/2} = 1.28 \times 10^{-9}$ (cc./molecule sec.)^{1/2}.

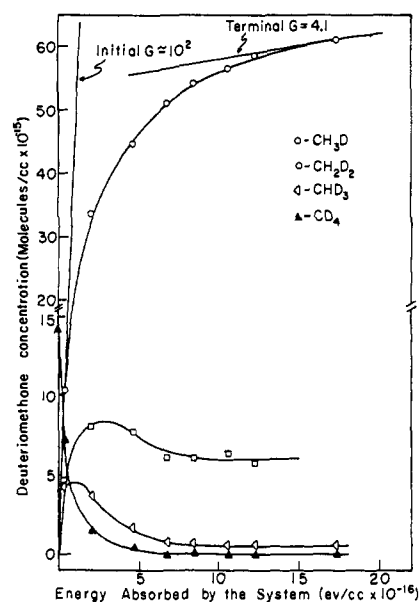


Figure 1. Deuteriomethane concentration vs. dosage.

The neutralization rate constant for CH_5^+ has not been reported. However, from other neutralization steps in simple systems,^{9,10} k_9 may be assumed to be $\approx 10^{-6}$ cc./molecule sec. Employing this value, we find k_5 to be $\approx 1 \times 10^{-12}$ cc./molecule sec.

To further substantiate this mechanism, the $\text{D}_2/\text{TD}-\text{CH}_4/\text{CD}_4$ system was studied at -78° . The initial rates of formation and disappearance of CH_3D and CD_4 , respectively, are equal to those observed at 25°. Steady-state treatment of the proposed mechanism provides that the relation $E_5 - E_9/2 = 0$ is valid within experimental error for our choices of dosage rate and CH_4 concentration provided that k_3/k_9 is greater than 10^{-8} (i.e., k_3 must presumably be of the order 10^{-14} or greater). Thus, one may conclude that the proton-transfer reactions (eq. 5) and the neutralization reactions (eq. 9) require no thermal activation subject to the condition that both sets require nonzero but approximately equal activation energies. Considering the nature of the two the latter appears quite unlikely, and we conclude that neither must be thermally activated.

Additional support for the proton-transfer mechanism is provided by the effect of the presence of NH_3 ,

(9) S. Takeda and A. A. Dougal, *J. Appl. Phys.*, **31**, 412 (1960).

(10) J. P. Doering and B. H. Mahan, *J. Chem. Phys.*, **36**, 669 (1962).

an efficient proton scavenger.¹¹ Our data indicate that a trace of NH₃ (1.5 mole %) completely stops the disappearance of CD₄. This effect is similar to that of Xe in the radiation-induced H₂-D₂ exchange.² Preliminary experiments indicate that Xe is not effective as a proton scavenger in the CH₄-D₂ system. Findings to date indicate that proton-transfer efficiencies may be ranked in the order NH₃ > CH₄ > Xe > D₂, and that this order may be the same as that for the proton affinities of these molecules. Judicious use of NH₃ to block ionic reactions in the D₂-TD-CH₄ system may permit accurate evaluation of the temperature coefficient for the atomic exchange reaction. Work directed toward establishment of a more inclusive scale of relative proton-transfer efficiencies and toward elucidation of the atomic and free-radical exchange mechanism for CH₄ and D₂ is in progress.¹²

(11) M. A. Bonin, W. R. Busler, and F. Williams, *J. Am. Chem. Soc.*, **84**, 4355 (1962).

(12) This work is partially supported by U.S.A.E.C. Contract AT-(11-1)-116.

(13) Captain, U.S.A.F., A.F.I.T. Program 1961-1965.

R. H. Lawrence, Jr.,¹³ R. F. Firestone

Department of Chemistry, The Ohio State University
Columbus 10, Ohio

Received March 22, 1965

The Heat of Formation of Xenon Tetroxide¹

Sir:

The preparation and some properties of XeO₄ have been recently described.^{2,3} In the present work, the heat of explosive decomposition of the gas to its constituent elements at 25° has been measured.

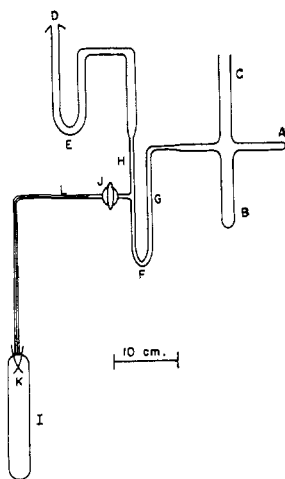


Figure 1. Preparation and explosion system.

The preparation was performed essentially according to the procedure previously given,³ using the glass apparatus shown in Figure 1. Anhydrous sodium perxenate, 40 to 80 mg. (Peninsular ChemResearch, Gainesville, Fla.), was placed at A and *ca.* 5 ml. of

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. L. Huston, M. H. Studier, and E. N. Sloth, *Science*, **143**, 1161 (1964).

(3) H. Selig, H. H. Claassen, C. L. Chernick, J. G. Malm, and J. L. Huston, *Science*, **143**, 1323 (1964).

previously boiled sulfuric acid at B; the system was then sealed off at C and evacuated overnight through D with a -196° bath at E. The apparatus was then inclined slightly counterclockwise, a 0° bath placed at B and a -126° bath at F, and the salt slowly added to the acid by occasional tapping at A over a period of *ca.* 0.5 hr. The system was then sealed off at G, a -196° bath placed at F, and the system again sealed at H. The 90-ml. explosion cell I was then placed in the aneroid copper-block calorimeter previously described.⁴ After recording of the foredrift, the -196° bath was removed from F and a warm-air blower, *ca.* 50 cm. distant, was played on trap F. The solid in the trap was seen to disappear in about 40 sec., and, about 15 sec. later, stopcock J was closed and the gas immediately exploded by passing a spark from a 0.1- μ f. capacitor at 600 v. across the loosely contacting tungsten electrodes K. A blue flash was seen to pass up the 1-mm. i.d. capillary from I to J. About 1.5 min. later, the capillary was sealed off at L.

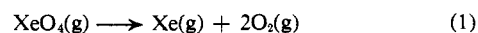
After the calorimetric measurement, the cell was attached to a gas-measurement line and the oxygen was transferred through three traps at -196° to a buret by means of a Toepler pump. The third trap was then warmed to -78° and the first two to room temperature to determine the xenon. The third trap was then warmed to room temperature; gas, probably mostly water, amounting to from 0.2 to 2% of the xenon was found. The oxygen and xenon were analyzed mass spectrometrically; a little xenon was found in the oxygen and a little carbon dioxide in the xenon. Appropriate corrections were applied to the measured amounts.

Of 24 preparations performed, 15 detonated in the trap F during warming, 2 failed to explode upon sparking, perhaps owing to very rapid previous nonexplosive decomposition to the elements, and the gas from 2 runs was lost after a successful explosion. Results for the successful runs are given in Table I. The yield of

Table I

Run	<i>q</i> , cal.	μ moles		$-\Delta H_f$, kcal. mole ⁻¹
		O ₂	Xe	
1	7.17	92.4	45.7	154.2
2	4.58	58.9	29.3	154.2
3	7.54	98.2	49.0	152.0
4	6.33	80.9	40.8	154.0
5	6.56	84.7	42.4	152.9

XeO₄ in the preparations ranged from 20 to 35%. The oxygen:xenon ratios found range from 1.984 to 2.022, equal to the theoretical value of 2 within experimental limits. The average of the xenon and one-half of the oxygen is used to calculate ΔH_f . nRT is subtracted from q to correct for the pV work done by the entering gas, and $2RT$ is subtracted from q_{cor}/n to convert from $-\Delta E$ to $-\Delta H$. The average is -153.5 for ΔH° of the reaction



or +153.5 for $\Delta H_f^\circ(\text{XeO}_4, \text{g})$.

Huston, *et al.*,² observed a nonexplosive decomposition of highly variable rate, yielding at least partly

(4) S. R. Gunn, *Rev. Sci. Instr.*, **35**, 183 (1964).