electron would be expected to move in a non-localized orbital, it does not appear to have been previously observed for the case of magnetic electrons associated with a normal paramagnetic atom.

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RECEIVED MAY 9, 1956

THE STRONG ACID BEHAVIOR OF DECABORANE

Sir:

Decaborane, in sharp contrast to the lower boranes, dissolves in alcohols, water–alcohol, water–dioxane and other protolytic solvents without rapid hydrolysis[1]; further, the rate of hydrogen evolution as observed by H. C. Beachell and W. A. Mosher[2] for the alcoholysis of decaborane exhibits a marked induction period. These observations suggest that a reasonable stable intermediate, a precursor to the hydrogen-producing reactions, is formed.

Consistent with these observations we have noted that the solution of decaborane in these solvents produces a strong monoprotic acid without the evolution of hydrogen and that decaborane is recoverable in part from such solutions. Typically, the titration of 122 mg. (1.00 millimole) of decaborane (approx. 95% pure) dissolved in 75% ethyl alcohol–water with 0.10 *N* sodium hydroxide was followed potentiometrically. The titration curve so obtained was characteristic of a strong monoprotic acid, the end-point being observed after the addition of 0.96 milliequivalent of base. Back titration with aqueous hydrochloric acid reproduced the same titration curve. That the decaborane structure is probably not destroyed in the formation of the strong acid is demonstrated by the recovery of decaborane (identified by melting point and mixed melting point, 97–98°) from alkaline water or alcohol–water solution in 35% yield by acidification. A large fraction of the decaborane apparently is lost through hydrolysis or alcoholysis as indicated by vigorous evolution of gas.

The formation of the strong acid is sufficiently slow so that its rate of growth can be followed potentiometrically, spectrophotometrically or conductimetrically. The last method, in 75% water–dioxane, yielded results sufficiently satisfactory for kinetic treatment. The rate ($-\log k_{9.4} = 3.16$; $-\log k_{15.2} = 3.00$; $-\log k_{21.5} = 2.71$; $-\log k_{25.5} = 2.57$) is first order in decaborane and independent of hydrogen ion. From the data is derived $\Delta H^{\pm} = 14.2$ kcal. mole^{-1}.

It is proposed that the hydrogen ion originates either by reaction between decaborane and the solvent

$$B_{10}H_{14}(\text{soln.}) + H_2O = [B_{10}H_{14}OH]^-(\text{soln.}) + H^+(\text{soln.})$$

or by loss of a proton from the decaborane

$$B_{10}H_{14}(\text{soln.}) = [B_{10}H_{13}]^-(\text{soln.}) + H^-(\text{soln.}).$$

Either process would fit the observed kinetics. Deuterium exchange and kinetic experiments which should help to distinguish between them are now in progress.

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RECEIVED MAY 31, 1956

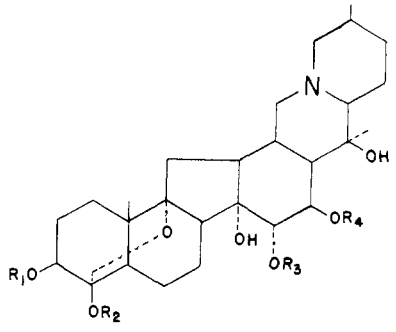
(1) W. H. Hill and M. S. Johnson, *Anal. Chem.*, **27**, 1300 (1955); H. C. Beachell and T. R. Meeker, THIS JOURNAL, **78**, 1796 (1956).

(2) H. C. Beachell and W. A. Mosher, private communication.

ZYGADENUS ALKALOIDS. VII. ON THE STRUCTURE OF ZYGADENINE

Sir:

The alkamine zygadenine[1] ($C_{27}H_{43}O_7N$) and its ester alkaloid derivatives have been shown to occur, alongside germine and its esters, in several species of *Zygadenus*[1–4] and *Veratrum*.[5,6] I wish to report evidence for structure I for zygadenine.



I, $R_1 = R_2 = R_3 = R_4 = H$
II, $R_1 = R_3 = R_4 = Ac$; $R_2 = H$
III, $R_1 = R_2 = R_3 = R_4 = Ac$
V, $R_1 = R_4 = Ac$; $R_2 = R_3 = H$
VI, $R_1 = Ac$; $R_2 = R_3 = R_4 = H$

The order of stability of the zygadenine isomers [zygadenine (3-β-hydroxy-4,9-hemiketal)<isozygadenine[7] (3-β-hydroxy-4-keto-9-α-hydroxy-A/B *trans*)<pseudozygadenine (3-α-hydroxy-4,9-hemiketal)][2] parallels that of the veracevine isomers and differs from that of the germine series.[8] Zygadenine forms a triacetate (II) upon acetylation with acetic anhydride alone; acetylation with acetic anhydride–pyridine affords a tetraacetate (III).[3] Acetylation of zygacine acetonide[3] (zygadenine-14,15-acetonide-3-acetate) with acetic anhydride yields zygadenine-14,15-acetonide-3,16-diacetate (IV), m.p. 271–272° dec., $[\alpha]^{23}D$ − 29° (py.). Found: C, 66.33; H, 8.35; acetyl, 13.61. Hydrolysis of IV with dilute mineral acid affords zygadenine-3,16-diacetate (V), m.p. 255–257° dec., $[\alpha]^{23}D$ − 50° (py.). Found: C, 64.69; H, 8.17; acetyl, 14.83; equiv. wt., 582. Periodate titrations indicate the following uptakes: zygadenine (I), 3 mole; zygacine[3,4] (VI), 2 mole; zygadenine diacetate (V), 1 mole; zygadenine triacetate (II), 0 mole; zygacine acetonide, 0 mole. Formulation I for zygadenine was first conceived as a reasonable rationalization of the above facts.

(1) F. W. Heyl, F. E. Hepner and S. K. Loy, THIS JOURNAL, **35**, 258 (1913); F. W. Heyl and M. E. Herr, *ibid.*, **71**, 1751 (1949).

(2) S. M. Kupchan and C. V. Deliwala, *ibid.*, **75**, 1025 (1953).

(3) S. M. Kupchan, D. Lavie and R. D. Zonis, *ibid.*, **77**, 689 (1955).

(4) S. M. Kupchan, C. V. Deliwala and R. D. Zonis, *ibid.*, **77**, 755 (1955).

(5) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **36**, 1570 (1953).

(6) M. W. Klohs, M. D. Draper, F. Keller, S. Koster, W. Malesh and F. J. Petracek, THIS JOURNAL, **75**, 4925 (1953).

(7) I propose the name isozygadenine for the amorphous carbonyl-containing isomer of zygadenine described in reference 2.

(8) S. M. Kupchan and C. R. Narayanan, *Chemistry and Industry*, in press.

Strong evidence in favor of structure I for zygadenine has now been obtained by interrelation of zygadenine with germine. Treatment of 7-ketogermine-3,16-diacetate[8] in methanol with 1,3-propanedithiol and anhydrous hydrogen chloride yields 7-ketogermine-3,16-diacetate-propylene thioketal hydrochloride (VII), m.p. 265–266° dec., $[\alpha]^{23}D$ − 5° (py.); $\lambda_{max.}^{alc.}$ 246 mμ (ε 600). Found: C, 56.86; H, 7.80; S, 9.13; Cl, 5.11. Raney nickel desulfurization of VII affords zygadenine-3,-16-diacetate (V), characterized by mixed melting point and infrared spectral comparison with the authentic sample.[9]

(9) This work was supported by a grant from the National Heart Institute of the National Institutes of Health (H-2275).

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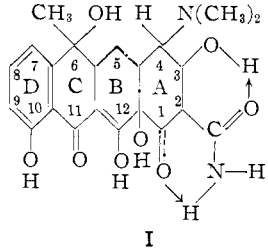
RECEIVED APRIL 20, 1956

ON THE NATURE OF THE REVERSIBLE ISOMERIZATIONS OCCURRING IN THE TETRACYCLINE FAMILY

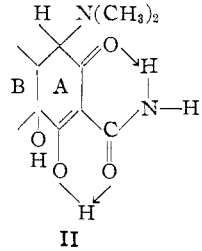
Sir:

We have recently reported that each of the known tetracyclines can be reversibly converted to a new, isomeric substance. These new substances were named the quatrimycins.[1] We now wish to report further studies on the nature of these reversible changes.

Consideration of the ultraviolet spectral differences between pair members[1,2] and of the conditions permitting and preventing isomerization[1] makes it most likely that the isomerization involves only a change in the configuration of C.4. However, changes in the orientation of the carboxamide group (I and II below), as suggested previously[3] to



I



II

explain the existence of α- and β-apoterramycin, are not entirely excluded. In an attempt to exclude the latter possibility, tetracycline[4] and quatrimycin were converted to the benzenesulfonyl nitriles[3] and chlorotetracycline[4] and chloroquatrimycin were converted to the unsubstituted nitriles.[5] Benzenesulfonyltetracyclinonitrile dimethylformamide (DMF) solvate: $[\alpha]^{25}D$ −416° (0.5% in DMF); m.p., dec. above 210°; *Anal.* Calcd. for $C_{31}H_{34}N_3SO_{10}$: C, 58.20; H, 5.31; N, 6.56; S, 5.00. Found: C, 58.25; H, 5.24; N, 5.93; S, 4.93. Benzenesulfonylquatrimycinonitrile monohydrate: $[\alpha]^{25}D$ −336° (0.5% in DMF); m.p., dec. above 200°; *Anal.* Calcd. for $C_{28}H_{29}N_2SO_{10}$: C, 57.40; H, 4.96; N, 4.78; S, 5.47. Found: C, 57.51; H, 5.29; N, 4.74; S, 4.97. Chlorotetracyclinonitrile: $[\alpha]^{25}D$ −338° (0.5% in DMF); m.p., dec. above 220°; *Anal.* Calcd. for $C_{22}H_{21}N_2O_7Cl$: C, 57.30; H, 4.56; N, 6.07; Cl, 7.69. Found: C, 56.99; H, 5.01; N, 6.37; Cl, 7.37. Chloroquatrimycinonitrile monohydrate: $[\alpha]^{25}D$ −300° (0.5% in DMF); m.p., dec. above 190°; *Anal.* Calcd. for $C_{22}H_{23}N_2O_8Cl$: C, 55.10; H, 4.80; N, 5.85; Cl, 7.40. Found: C, 54.91; H, 4.76; N, 5.72; Cl, 7.89. The members of each nitrile pair are isomeric and distinguishable[6] but none of these four compounds could be isomerized, although many conditions were tried. Thus, the carboxamide group, though not essential to the existence of isomeric pairs, does play a part in the ready interconversion of the parent compounds. Interconversion of the nitrile pair members under conditions equilibrating the tetracyclines, had it been possible, would have provided a simple, certain proof that the sulfonyl chloride reagents had acted in completely parallel ways on both members of the parent pairs. Lack of this proof weakens somewhat the argument that distinguishable sulfonyl chloride reaction products have eliminated the carboxamide orientation possibility.

Further work to establish epimerization at C.4 took the form of eliminating the asymmetry at C.4 by reductive removal of the 4-dimethylamino group. Zinc and glacial acetic acid at 30° for six hours can accomplish this.[2] However, we have found that both tetracycline and quatrimycin are completely equilibrated in 2.5 hours in glacial acetic acid–zinc acetate at 25°. Thus, even if reduction under these conditions yielded identical desdimethylamino products from both members of an isomeric pair, no distinction could be drawn between the alternatives of isomerization during reduction and of configuration at C.4 being the difference separating the pair members. This difficulty was resolved by preparing the methiodides of tetracycline and quatrimycin and reducing them in 50% aqueous acetic acid.[7] Tetracycline methiodide: $[\alpha]^{25}D$ −198° (0.5% in 0.03*N* HCl); m.p., 178–180° (dec.); *Anal.* Calcd. for $C_{23}H_{27}N_2O_8I$: C, 47.11; H, 4.64; N, 4.71; I, 21.64. Found: C, 47.38; H, 4.58; N, 4.91; I, 22.15. Quatrimycin methiodide: $[\alpha]^{25}D$ −265° (0.5% in 0.03 *N* HCl); m.p., 161–162° (dec.); *Anal.* Found: C, 47.32; H, 4.74; N, 4.64; I, 21.29. The two methiodides were isomeric, distinguishable, and reversibly interconvertible. However, neither methiodide was measurably isomerized after remaining four hours in a reduction solvent consisting of 50% aqueous acetic acid with four equivalents of zinc acetate;

(1) A. P. Doerschuk, B. A. Bitler and J. R. D. McCormick, THIS JOURNAL, **77**, 4687 (1955).

(2) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

(3) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953).

(4) The trademarks of the American Cyanamid Co. for tetracycline and chlorotetracycline are Achromycin and Aureomycin, respectively.

(5) This method, involving reaction with methanesulfonyl chloride and pyridine, is that of R. Wilkinson, Research Division, American Cyanamid Company, who had used it previously to prepare the nitrile of chlorotetracycline.

(6) Ultraviolet and infrared spectra and solubilities were used as criteria of distinguishability.

(7) The methods of methiodide preparation and reduction and a sample of tetracycline methiodide were obtained from J. Boothe, Research Division, American Cyanamid Co.