clinical evaluation indicates that V and VI have activities similar to I and II.

DAVID GOULD
CHEMICAL RESEARCH DEPARTMENT — ELLIOT L. SHAPIRO, HERSHEL L. HERZOG, MARGARET J. GENTLES, E. B. HERSHBERG
INDUSTRIAL MICROBIOLOGY DEPARTMENT — WILLIAM CHARNEY, MARILYN GILMORE
BIOCHEMISTRY DEPARTMENT — SIBYLLE TOLKSDORF
SCHERING CORPORATION — MILTON EISLER
BLOOMFIELD, N. J. — PRESTON L. PERLMAN
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS — MAURICE M. PECHET

RECEIVED DECEMBER 21, 1956

SYNTHESIS OF 6-(1,2-DICARBOXYETHYLAMINO)-9-β-D-RIBOFURANOSYLPURINE AND THE STRUCTURE OF ADENYLOSUCCINIC ACID[1]

Sir:

The recent isolation[2] from mouse and rabbit livers of adenylosuccinic acid (AMPS) supports evidence from enzymatic studies[3,4] that AMPS is an intermediate in the biosynthesis of adenylic acid (AMP) from inosinic acid. Carter and Cohen[5a] assigned to AMPS the structure 6-(1,2-dicarboxyethylamino) - 9 - ribofuranosylpurine - 5′-phosphate on the basis of its physical properties, enzymatic reactions, and its acid degradation to authentic 6-(1,2-dicarboxyethylamino)-purine[5b].

6-(1,2-Dicarboxyethylamino)-9-β-D-ribofuranosylpurine (I) has been synthesized by an unambiguous route. 6-Methylmercapto-9-β-D-ribofuranosylpurine[6] (1.68×10^{-3} mole), *dl*-aspartic acid (1.68×10^{-2} mole), NaOH (3.02×10^{-2} mole), and water (7 cc.) were refluxed for 20 hours; methyl mercaptan was evolved; HCl (3.02×10^{-2} mole) was added. Paper chromatograms of the solution run in solvent B[7] were sprayed to detect acidic components[8] and *cis*-glycol systems[9]; I was identified as an ultraviolet light-absorbing spot which reacted positively in both tests. The solution was chromatographed on Dowex-1 (formate) (100 cc.). Elution with water (2 l.) followed by 0.2 *N* formic acid (1.6 l.) removed aspartic acid and ultraviolet light-absorbing by-products. Evaporation at 0.5 mm. of a 1 *N* formic acid eluate gave crude I as a gum (153 mg., 24%). Rechromatography at 3° on Dowex-1 (formate) (60 cc., height 17 cm.), employing gradient elution (2 *N* formic acid in reservoir; mixer volume, 1 liter), effected elution of a non-glycosidic substance[10] just prior to I. The product (75 mg.) was chromatogramed on paper in solvent A[7] to remove traces of an unidentified nucleoside (R_f 0.27). Elution with methanol followed by crystallization from methyl cyanide gave a white powder which in 2 cc. of ethanol deposited microplates of I (32 mg., m.p. 235–245° dec.) after 4 days at 25°. Calcd. for $C_{14}H_{17}N_5O_8$: C, 43.86; H, 4.47; N, 18.27. Found[11]. C, 43.81; H, 4.54; N, 18.20. Paper chromatography[7] and paper electrophoresis[12] showed no other components. Potentiometric titration revealed ionizing groups of pK_a 2.2 (±0.1), 5.1 (±0.1), and a third of intermediate pK_a; λ_{max} (*p*H 0.1) 268 mμ (A_M 15,500 ± 1000), (*p*H 8.2) 269 mμ (A_M 17,600 ± 1000). AMPS possesses very similar spectroscopic and ionization constants.[5c]

Treatment of AMPS[13] with phosphatases[14] yielded a nucleoside[15] (λ_{max} 269 mμ at *p*H 8.2) indistinguishable from I by paper chromatography[7] or electrophoresis.[12]

AMPS was heated in 0.1 *N* H_2SO_4 for 4 hours at 100°. The solution was neutralized with ammonia and chromatogramed on paper in four solvent systems,[16] together with a similar hydrolysate from AMP and samples of D-ribose-5′-phosphate, D-ribose, and Na_2HPO_4. Duplicates from each hydrolysate yielded evidence for much D-ribose-5′-phosphate,[17,18] traces of D-ribose[17] and of inorganic phosphate.[18] AMPS reacted as an unsubstituted *cis*-glycol in the periodate test.[9]

These findings afford strong evidence that AMPS is the 5′-phosphate of I, in agreement with the structure previously proposed.[5a]

The author thanks Drs. George Bosworth Brown and C. E. Carter for valuable discussions.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service, Grant No. C-471, and the Atomic Energy Commission, Contract No. AT(30-1)-910.

(2) W. K. Joklik, *Biochem. Biophys. Acta*, **22**, 211 (1956).

(3) R. Abrams and M. Bentley, THIS JOURNAL, **77**, 4179 (1955).

(4) I. Lieberman, *ibid.*, **78**, 251 (1956).

(5) (a) C. E. Carter and L. H. Cohen, *ibid.*, **77**, 499 (1955); (b) C. E. Carter, *Fed. Proc.*, **15**, 230 (1956); (c) C. E. Carter and L. H. Cohen, *J. Biol. Chem.*, **222**, 17 (1956).

(6) A. Hampton, J. J. Biesele, A. E. Moore, and G. B. Brown, THIS JOURNAL, **78**, 5695 (1956).

(7) R_f values (ascending solvents, Schleicher and Schuell No. 597 paper): (A) *n*-butanol 50, acetic acid 20, water 30, *n*-butyl acetate 30 (0.40); (B) *n*-butanol 50, acetic acid 25, water 25 (0.59); (C) 5% Na_2HPO_4, *iso*amyl alcohol (C. E. Carter, THIS JOURNAL, **72**, 1466 (1950)) (0.90).

(8) The reagent was a 0.1% solution of brom thymol blue in 0.02 *N* NaOH.

(9) J. G. Buchanan, C. A. Dekker and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(10) This material, λ_{max} 276 in 0.1 *N* HCl, was probably the aglycone[5b] of I and could be detected in the presence of I on chromatograms run in pyridine–water (65:35).

(11) Analysis by J. F. Alicino, Metuchen, N. J.

(12) Migration distances towards the anode (Whatman 3MM paper, 800 volts, 0.04 *M* buffer) were: *p*H 4.7 (acetate–HCl buffer), 9.5 cm. in 1 hr.; *p*H 7.3 (phosphate), 10.5 cm. in 50 min.; *p*H 10.1 (glycine–NaOH), 8.5 cm. in 35 min.

(13) Kindly provided by Dr. C. E. Carter.

(14) Crudesnake venom phosphatases at *p*H 8.1, or human prostatic phosphatase at *p*H 5.4 caused complete conversion of AMPS in 24 hours at 37°.

(15) Purified by paper chromatography in solvent B.[7]

(16) *n*-Butanol–acetic acid–water (50:20:35); 1% aqueous $(NH_4)_2SO_4$–isopropyl alcohol (1:2) (N. Anand, V. M. Clark, R. H. Hall, and A. R. Todd, *J. Chem. Soc.*, 3665 (1952)); acetone–30% acetic acid (1:1) (S. Burrows, F. S. M. Grylls and J. S. Harrison, *Nature*, **170**, 800 (1952)); pyridine–ethyl acetate–water (1:2:2) (S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

(17) S. M. Partridge, *Nature*, **164**, 443 (1949).

(18) C. S. Hanes and F. A. Isherwood, *ibid.*, **164**, 1107 (1949).

THE SLOAN-KETTERING DIVISION OF
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK 21, NEW YORK — ALEXANDER HAMPTON

RECEIVED DECEMBER 3, 1956

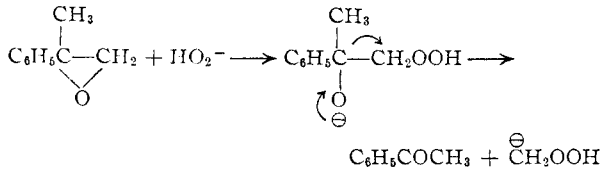
A CLEAVAGE REACTION INVOLVING α-METHYLSTYRENE OXIDE[1]

Sir:

It has been found that α-methylstyrene oxide (1,2-epoxy-1-methylethylbenzene) when allowed to

(1) This work was supported by the Air Research and Development Command under contract No. (AF 18(600)787) with the Ohio State University Research Foundation.

react with alkaline hydrogen peroxide in 90% methanol at room temperature gives an almost quantitative yield of acetophenone. The product obtained is most readily explained by the equation



$$C_6H_5COCH_3 + \overset{\ominus}{C}H_2OOH$$

α-Methylstyrene (b.p. 164–165°, n^{20}D 1.5384) was treated with N-bromosuccinimide and water to obtain the bromohydrin; α-methylstyrene oxide was then obtained by the action of aqueous sodium hydroxide on the bromohydrin.[2] Careful distillation of the product gave epoxide with the following properties: b.p. 84.5–85.5° (17 mm.), n^{20}D 1.5208 (lit.[3] b.p. 85° (17 mm.)), n^{20}D 1.5208. Calcd. for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.78; H, 7.29.

To 25 ml. of 90% methanol, 0.5 *N* in potassium hydroxide, was added 0.24 g. of epoxide and 5 ml. of 30% hydrogen peroxide. At the end of 48 hours an 85–90% yield of acetophenone was isolated as the 2,4-dinitrophenylhydrazone (m.p. and mixed m.p. 247–248°; lit.[4] m.p. 247–248°). Similar experiments were carried out in which potassium hydroxide and then hydrogen peroxide were eliminated from the reaction medium. In either case little if any acetophenone was produced.

(2) C. O. Guss and R. Rosenthal, THIS JOURNAL, **77**, 2549 (1955).
(3) R. Rothstein and J. Ficini, *Compt. rend.*, **234**, 1694 (1952).
(4) G. D. Johnson, THIS JOURNAL, **75**, 2720 (1953).

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY JOSEPH HOFFMAN
COLUMBUS, OHIO

RECEIVED OCTOBER 26, 1956

INTRAMOLECULAR VAN DER WAALS-LONDON COHESIONS IN BUTADIENE AND BENZENE

Sir:

The idea of (localized) electrons in neighboring bonds within a molecule oscillating in phase with each other has been put forward repeatedly in connection with the electronic spectra of compounds containing conjugated double bonds.[1,2,3] London's explanation of van der Waals attraction between molecules[4] is based on a similar idea, *viz.*, the interaction between oscillating molecular dipoles. In the simplest possible model, two identical spherically symmetrical molecules, a distance R apart, each having a dipole oscillation of frequency ν_0 and a corresponding polarizability α, interaction produces six modes of oscillation, one in-phase and one out-of-phase along each axis, of frequencies $\nu = \nu_0\sqrt{1 \pm q}$, where $q_{par.} = 2\alpha/R^3$, $q_{perp.} = \alpha/R^3$. The zero-point stabilization energy of the two interacting units, relative to the two isolated units (expanded to terms in q^4), is

$$U_0 = {}^1/_2h\Sigma\nu - 6 \times {}^1/_2h\nu_0 \doteq -{}^3/_4h\nu_0(\alpha^2/R^6 + \alpha^4/R^{12})$$

Similar interactions between identical bonds (or electron pairs) within a molecule, and weaker ones between dissimilar units, affect molecular properties ranging from chemical reactivities[5] to diamagnetic susceptibilities; these interactions are especially prominent if the molecule contains (highly polarizable) π-electrons and account for many effects conventionally explained by π-electron delocalization.[6]

Quantitative estimates of van der Waals–London cohesions based on the above approach[7] are possible only for systems possessing a high degree of regularity, such as polyenes. Butadiene is comparable with two ethylene molecules, benzene (assumed to have the Kékulé structure[8]) with three. The main cohesion energy, due to interaction of the logitudinal π-electron oscillations,[9] $U_{0(longit.)}$, is best obtained by evaluating q, the "effective" $2\alpha/R^3$, from spectrally observed absorption frequencies. The appropriate modes of oscillation and the spectral frequencies assigned to them are roughly[6] as shown in (I) to (VI). The frequencies of (II) and (III), and similarly those of (V) and (VI), are approximately related to the ethylene frequency ν_0 as $\nu_0\sqrt{1-q}$ and $\nu_0\sqrt{1+q}$.

(I) $CH_2{=}CH_2$ 57,310 cm.$^{-1}$ (II) $CH_2{=}CH{-}CH{=}CH_2$ 46,080 cm.$^{-1}$

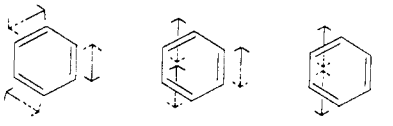
(III)[10] $CH_2{=}CH{-}CH{=}CH_2$?

For butadiene

$$U_{0(longit.)}{}^{11} \doteq -{}^1/_2hc \times 57{,}310 \times {}^1/_4\left[1 - \left(\frac{46080}{57310}\right)^2\right]^2 \doteq -2.7 \text{ kcal./mole}$$

this is considerably less than the cohesion energy obtained by Simpson's[12] wave-mechanical approach (5.5 kcal./mole).[6]

(IV)[10] (V) (VI)[10](?)



[13]38,460 cm.$^{-1}$ 50,000 cm.$^{-1}$?

For benzene

$$U_{0(longit.)}{}^{11} \doteq -{}^1/_2hc[(57310 - 38460) + 57310 \times {}^1/_4 \left\{1 - \left(\frac{50000}{57310}\right)^2\right\}^2] = -28 \text{ kcal./mole}$$

(1) D. Radulescu, *Ber.*, **64**, 2223 (1931).
(2) G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 273 (1939).
(3) W. Kuhn, *Helv. Chim. Acta*, **31**, 1780 (1948).
(4) F. London, *Trans. Far. Soc.*, **33**, 8 (1937), and references cited there.
(5) E. Spinner, *J. Chem. Soc.*, 1590 (1956).
(6) See E. Spinner, forthcoming publication, for detailed discussion.
(7) K. S. Pitzer and E. Catalano have just treated the paraffins successfully by a different approach (THIS JOURNAL, **78**, 4844 (1956)).
(8) For criticism of the concept of π-electron delocalization see A. Burawoy, "Contribution a l'Étude de la Structure Moleculaire," Desoer, Liege, 1948, p. 73, and references cited there.
(9) Other coördinated electron oscillations produce additional stabilizations.
(10) Transition forbidden.
(11) Accurate to terms in q^2.
(12) W. T. Simpson, THIS JOURNAL, **73**, 5363 (1951).
(13) A. Burawoy, *et al.*, attribute this band to a transition involving an electron migration around the ring (*J. Chem. Soc.*, 3721 (1955)).