COMMUNICATIONS TO THE EDITOR

THE SOLUBILITY OF HYDROGEN CHLORIDE AT LOW TEMPERATURES—A MEASURE OF THE BASIC PROPERTIES OF AROMATIC NUCLEI

Sir:

There is now considerable evidence that aromatic nuclei possess basic properties. Klatt[1] observed that aromatic compounds dissolve in liquid hydrogen fluoride, whereas saturated hydrocarbons do not. Winstein and Lucas[2] and, more recently, Keefer and Andrews[3] attribute complex formation between silver ion and aromatic hydrocarbons to the basic properties of the aromatic nuclei. Fairbrother[4] correlated changes in the apparent dipole moments of iodine in several hydrocarbon solvents with changes in the probable donor character of the π electrons in the hydrocarbon. Finally, the absorption spectra of solutions of iodine in aromatic hydrocarbons show changes which can also be correlated with the basic properties of the solvent.[5]

In the course of studies of the action of the catalyst couple, aluminum chloride–hydrogen chloride, on aromatic hydrocarbons at low temperatures, we have observed that the solubility of hydrogen chloride varies considerably with different aromatic hydrocarbons. The variation in solubility cannot be correlated with any of the usual physical properties of the solvent, but it can be correlated with the predicted variation in the basic properties of the compounds.

In order to investigate this phenomenon more carefully, we developed a method for measuring Henry's law constant with a precision of approximately 1 part in 500. Toluene is used as solvent. A solution of 10 moles of toluene and 1 mole of aromatic hydrocarbon is prepared. The solution is maintained at $-78.51°$ and small quantities of hydrogen chloride are introduced. Henry's law is followed over a wide range of concentration. From the observed pressures, the constant is calculated from the usual expression, $p = kx$, where p is the pressure of hydrogen chloride, x is its mole fraction and k is the desired constant.

The following values for k (in mm.) have been obtained: (1) trifluoromethylbenzene, 332; (2) chlorobenzene, 318; (3) benzene, 308; (4) toluene, 299; (5) *p*-xylene, 294; (6) *o*-xylene, 286; (7) *m*-xylene, 278; (8) pseudocumene, 272; (9) hemimellitene, 265; (10) mesitylene, 254.

It is apparent that the order of increasing solubility is identical with the order of increasing reactivity toward the usual electrophilic substituting agents. Therefore, Henry's law constant may be taken as a measure of the relative basicity of the ring. It is particularly interesting that the method is sufficiently sensitive to differentiate between the isomeric xylenes and trimethylbenzenes.

We are now applying the procedure to other benzenoid derivatives, polynuclear hydrocarbons, heterocyclics and olefins. The data should be useful in giving a quantitative measure of the effect of structure on the relative basicities of these compounds.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

HERBERT C. BROWN
JAMES BRADY

RECEIVED JULY 28, 1949

(1) Klatt, *Z. anorg. allgem. Chem.*, **234**, 189 (1937); Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 293–294.

(2) Winstein and Lucas, THIS JOURNAL, **60**, 836 (1938).

(3) Abstracts of Papers Presented to the Division of Organic Chemistry at the 115th Meeting of the American Chemical Society, San Francisco, 1949, p. 47.

(4) Fairbrother, *J. Chem. Soc.*, 1051 (1948).

(5) Benesi and Hildebrand, THIS JOURNAL, **70**, 2832 (1948); **71**, 2703 (1949).

PROPARGYLGLYCINE: AN ACETYLENIC AMINO ACID ANTAGONIST[1,2]

Sir:

As part of a research program designed to get information concerning the basis for the preparation of specific metabolite antagonists, we prepared and studied the vinylene-type unsaturated amino acids, allylglycine, methallylglycine, crotylglycine and 2-amino-5-heptenoic acid.[3] Since allylglycine was a potent inhibitor of the growth of bacteria and yeast, we deemed it desirable to prepare the corresponding acetylenic amino acid, propargylglycine. In this communication we wish to report the synthesis and preliminary microbial-growth inhibitory properties of propargylglycine.

Diethyl Propargylformamidomalonate.—To a solution containing 0.92 g. (0.04 g. atom) of sodium dissolved in 75 ml. of absolute alcohol was added 8.12 g. (0.04 mole) of diethyl formamidomalonate.[4] Five grams (0.042 mole) of propargyl bromide[5] in 20 ml. of ethanol was added and refluxed for eighteen hours. After concentration to dryness, the residue was taken up in a mixture of chloroform and water. The residue from the chloroform was recrystallized from water. The diethyl propargylformamidomalonate melted at 69–70°, and the yield was 90%. An analytical sample was obtained from di-*n*-butyl ether, m. p. 71–72°.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22; N, 5.81. Found: C, 54.85; H, 6.34; N, 5.59.

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) The authors gratefully acknowledge the technical assistance of Mrs. Ann E. Johnson and Mr. Robert P. Martin.

(3) (a) Dittmer, Goering, Goodman and Cristol, THIS JOURNAL, **70**, 2499 (1948); (b) Goering, Cristol and Dittmer, *ibid.*, **70**, 3310, 3314 (1948).

(4) A. Galat, *ibid.*, **69**, 965 (1947).

(5) A. Kirrmann, *Bull. soc. chim.*, IV, **39**, 698 (1926).

Propargylglycine.—The diethyl propargylformamidomalonate was hydrolyzed by refluxing 2.4 g. (0.01 mole) of the ester with 24 ml. of 8% sodium hydroxide for four hours. The mixture was diluted to 100 ml. with water and passed through a column of Duolite C-10H which removed all the base. The effluent was subsequently passed through a column of Duolite A-2 which removed the formic acid produced. The resulting solution was concentrated *in vacuo*, decolorized with Darco G-60, and on addition of acetone, the amino acid crystallized. The yield was 88.5%. An analytical sample of propargylglycine was obtained from water and acetone, m. p. 243° with decomposition.

Anal. Calcd. for $C_5H_7O_2N$: C, 53.09; H, 6.24; N, 12.39. Found: C, 53.24; H, 6.20; N, 12.47.

Norvaline.—Hydrogenation of 113 mg. (0.001 mole) of propargylglycine in the presence of Adams catalyst, at 28° and 1 atmosphere, required 0.00207 mole (104% of theoretical) of hydrogen and produced 100 mg. of norvaline, which melted with decomposition at 297° in a sealed tube; the benzoyl derivative prepared as above, m. p. 150–151°.

Microbiological Tests.—Propargylglycine was tested as an inhibitor of the growth of *Escherichia coli*, strain 9723 and *Saccharomyces cerevisiae*, strain 139.[6] To inhibit the growth of these microörganisms, to 50% of normal growth, required 4 micrograms per 7.5 ml. of medium for *S. cerevisiae* and 65 micrograms for *E. coli*. According to these data propargylglycine is more active than allylglycine for yeast but less active for the inhibition of *E. coli*.

(6) The methods employed and the test organisms were the same as those previously described.[5a]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLORADO
HERMAN GERSHON
JOHN S. MEEK
KARL DITTMER

RECEIVED AUGUST 5, 1949

N[10]-NITROSOPTEROYLGLUTAMIC ACID

Sir:

The action of nitrous acid upon 2-aminopteridines has led to destruction of the ring system,[1] desamination in the 2-position,[2] and simultaneous desamination of the 2-position and nitrosation on the nitrogen atom in the 10-position of pteroic acid.[3] "Folic acid" concentrates from natural sources[4] were inactivated by nitrous acid under the conditions of the Van Slyke determination.[5] These experiments involved the use of excess nitrous acid and temperatures ranging from "room temperature" to 100° or higher.

We wish to report that pteroylglutamic acid in cold hydrochloric acid solution reacts quantitatively with one mole of nitrous acid to form N[10]-nitrosopteroylglutamic acid, which precipitates from the reaction mixture as a white solid.

N[10]-Nitrosopteroylglutamic acid gives a positive Liebermann nitroso reaction. The nitroso group can be removed by treatment with phenol and hydrochloric acid, and pteroylglutamic acid thus regenerated.

Under substantially the same conditions, the following give N[10]-nitroso compounds: pteroyl-α-glutamylglutamic acid[6]; pteroyl-γ-glutamyl-γ-glutamylglutamic acid,[7] 9-methylpteroylglutamic acid,[8] 4-aminopteroylglutamic acid,[9] 2-dimethylaminopteroylglutamic acid,[10] and 4-(1-piperidyl)-pteroylglutamic acid.[10]

Neither 2-amino-4-hydroxy-6-methylpteridine,[11] 2,4-diamino-6-methylpteridine,[9b] nor N[10]-methylpteroylglutamic acid[12] react appreciably with nitrous acid under these conditions.

In a typical experiment, 4.4 g. of pteroylglutamic acid (90% purity,[13] 0.5% *p*-aminobenzoylglutamic acid, 8% H_2O) was dissolved in 50 ml. of concentrated hydrochloric acid, and cooled to 5–10° by the addition of ice. Then 0.7 g. of sodium nitrite dissolved in a little water was added slowly. A white precipitate formed, which was filtered, washed, and dried to give 3.2 g. of N[10]-nitrosopteroylglutamic acid. One gram of this dissolved in 25 ml. of 5 *N* sodium hydroxide was clarified with activated charcoal. On standing the sodium salt crystallized. It was collected, dissolved in water and precipitated with acid, filtered, washed, and dried two hours at 100° (2 mm.). *Anal.* Calcd. for $C_{19}H_{18}N_8O_7$: C, 48.5; H, 3.83; N, 23.8. Found: C, 48.9; H, 4.77; N, 24.05 (corrected for 3.8% ash).

Through the courtesy of our colleagues, Dr. B. L. Hutchings, and Dr. J. J. Oleson, of the Lederle Laboratories Division, American Cyanamid Company, N[10]-nitrosopteroylglutamic acid has been tested in a preliminary way in the nutrition of *S. faecalis* R and the chick, and in both cases appears to be equivalent to pteroylglutamic acid.

(1) Schopf and Kottler, *Ann*, **539**, 134 (1939).
(2) Wieland, *et al.*, *ibid.*, **507**, 245 (1933); Wittle, *et al.*, THIS JOURNAL, **69**, 1780 (1947); Taylor and Cain, *ibid.*, **71**, 2538 (1949).
(3) Wolf, *et al.*, *ibid.*, **69**, 2758 (1947).
(4) Mitchell and Williams, *ibid.*, **66**, 272 (1944).
(5) Van Slyke, *J. Biol. Chem.*, **16**, 121 (1913).
(6) Mowat, *et al.*, THIS JOURNAL, **70**, 1096 (1948).
(7) Boothe, *et al.*, *ibid.*, **70** 1099 (1948).
(8) Hultquist, *et al.*, *ibid.*, **71**, 619 (1949).
(9) (a) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947) (b) Seeger, *et al.*, *ibid.*, **71**, 1753 (1949).
(10) Roth, Smith and Hultquist, in press.
(11) Mowat, *et al.*, THIS JOURNAL, **70**, 17 (1948).
(12) Cosulich and Smith, *ibid.*, **70**, 1922 (1948).
(13) Hutchings, *et al.*, *J. Biol. Chem.*, **168**, 705 (1947).

CALCO CHEMICAL DIVISION
AMERICAN CYANAMID COMPANY
BOUND BROOK, NEW JERSEY
DONNA B. COSULICH
JAMES M. SMITH, JR.

RECEIVED AUG. 15, 1949

STEROLS. VIII.[1] 17α-HYDROXYPROGESTERONE AND 17α-HYDROXY-11-DESOXYCORTICOSTERONE

Sir:

Recently we reported[1] the facile preparation of 16,17-oxidoprogesterone from 16,17-oxido-5-pregnene-3β-ol-20-one acetate (I). We now wish to record the use of I as an intermediate for a new and very simple partial synthesis of both 17α-hydroxyprogesterone and 17α-hydroxy-11-desoxycorticosterone acetate (V) (acetate of Reichstein's Compound S). The reactions as applied to the latter are schematically presented by formulas I → V. A treatment of 16,17-oxidoprogesterone

(1) For paper VII in this series see THIS JOURNAL, **71**, 756 (1949)