

did not follow the Langmuir equation at concentrations greater than 1:1,000. The adsorption of neither compound conformed to the Freundlich adsorption isotherm at high concentrations.

6. Benzalkonium chloride solutions showed an anomaly with respect to surface tension. This anomaly seemed to be related to the failure of the application of the Langmuir equation to the adsorption determinations of benzalkonium chloride.

7. Chemical and bacteriological tests indicated that 1 Gm. of talc inactivated approximately 5 mg. of cetylpyridinium chloride by irreversible adsorption.

REFERENCES

- (1) Einhorn, A., and Gottler, M., *Ann. Chem.*, **361**, 150(1908).
- (2) Jacobs, W. A., and Heidelberger, M., *J. Biol. Chem.*, **21**, 403(1915).
- (3) Domagk, G., *Deut. med. Wochschr.*, **61**, 829(1935).
- (4) Mueller, W. S., Bennett, E., and Fuller, J. E., *J. Dairy Sci.*, **29**, 751(1946).
- (5) Lesser, M. A., *Drug & Cosmetic Ind.*, **64**, 434 and 559 (1949).
- (6) Botwright, W. E., *Am. Perfumer Essent. Oil Rev.*, **61**, 361(1953).
- (7) Finnegan, J. K., and Dienna, J. A., *Soap Sanit. Chemicals*, **30**, 147(1954).
- (8) Warren, M. R., Becker, T. J., Marsh, D. G., and Shelton, R. S., *J. Pharmacol. Exptl. Therap.*, **74**, 401(1942).
- (9) Werner, H. W., and Thompson, C. R., *Federation Proc.*, **8**, 473(1949).
- (10) Alfredson, B. V., Stiefel, J. R., Thorp, F., Jr., Baten, W. D., and Gray, M. L., *THIS JOURNAL*, **40**, 263(1951).
- (11) Shelanski, H. A., *Soap Sanit. Chemicals*, **25**, 125(1949).
- (12) Lawrence, C. A., *Soap, Perfumery & Cosmetics*, **27**, 370(1954).
- (13) Lawrence, C. A., "Surface Active Quaternary Ammonium Germicides," Academic Press, Inc., New York, 1950, pp. 1, 40, and 145.
- (14) Ressugan, J. C. L., "Quaternary Ammonium Compounds in Chemical Sterilization," United Trade Press, Ltd., 24 Bride Lane, London, E. C. 4, 1951, pp. 14-24, 30-36, and 72.
- (15) Hart, F., and Huyck, C. L., *THIS JOURNAL*, **37**, 272 (1948).
- (16) Prusak, L. P., and Mattocks, A. M., *ibid.*, **38**, 67 (1949).
- (17) Doubleday, C., *Soap, Perfumery & Cosmetics*, **26**, 263, 455(1953).
- (18) Lewis, W. F., *ibid.*, **28**, 642(1955).
- (19) Zussman, H. W., *Am. Perfumer Essent. Oil Rev.*, **47**, 54(1945).
- (20) Tice, L. F., and Pressman, R., *THIS JOURNAL*, **34**, 201(1945).
- (21) Miller, O. H., *ibid. Pract. Pharm. Ed.*, **13**, 657(1952).
- (22) Nixon, W., and Cheetham, M. W., *Pharm. J.*, **165**, 46(1950).
- (23) Joslyn, D. A., Yaw, K., and Rawlins, A. L., *THIS JOURNAL*, **32**, 49(1943).
- (24) Barker, H. E. R., *Australasian J. Pharm.*, **29**, 801 (1948).
- (25) Putnam, F. W., and Neurath, H., *J. Am. Chem. Soc.*, **66**, 692(1944).
- (26) Glassman, H., *Ann. N. Y. Acad. Sci.*, **53**, 91(1950-51).
- (27) Matalon, R., Salton, M. R. J., and Cohen, M., *Nature*, **167**, 241(1941).
- (28) Swiss Patent, 276557; through *Chem. Abstr.*, **47**, 1341 (1953).
- (29) Valko, E. I., and Dubois, A. S., *J. Bacteriol.*, **47**, 15(1944).
- (30) Lawrence, C. A., *THIS JOURNAL*, **37**, 57(1948).
- (31) Baker, Z., Harrison, R. W., and Miller, B. F., *J. Exptl. Med.*, **74**, 621(1941).
- (32) Quisno, R., Gibby, I. W., and Foter, M. J., *Am. J. Pharm.*, **118**, 320(1946).
- (33) Hawkins, D., and Thompson, H. O., *THIS JOURNAL*, **42**, 424(1953).
- (34) Carkhuff, E. D., and Boyd, W., *ibid.*, **43**, 240(1954).
- (35) Weiser, H. B., "Colloid Chemistry," 2nd ed., John Wiley and Sons, New York, 1949, pp. 49, 68-88.
- (36) Adam, N. K., and Shute, H. L., *Trans. Faraday Soc.*, **34**, 758(1938).
- (37) Rose, G. R. F., Weatherburn, A. S., and Bayley, C. H., *Textile Research J.*, **21**, 427(1951).
- (38) Davies, G. E., *Pharm. J.*, **170**, 277(1953).

Stability of Atropine in Aqueous Solution*

By ALBERT A. KONDRITZER and PETER ZVIRBLIS

A kinetic study of the proton catalyzed hydrolysis of atropine has been carried out and the temperature dependency of this reaction established. The constants obtained for this reaction have been combined with those previously reported for the hydroxyl catalyzed reactions and an equation proposed to predict the half life of atropine undergoing hydrolysis at constant pH and temperature. The pH of minimum hydrolysis has been calculated and found to vary with temperature from pH 4.11 at 0° to pH 3.24 at 100°. Calculated half lives of atropine in solution over the region of pH 2 to 7 at temperatures from 20° to 100° are given.

WE ARE engaged in a program to identify and evaluate the factors involved in the deterioration of aqueous solutions of atropine and its salts. A previous study (1) of the chemical kinetics of the alkaline hydrolysis of atropine in aqueous solution has shown that the mechanism of this hydrolysis consists of two reactions: one involving the unprotonated (base) form, and the other the protonated (ionic) form of the alkaloid.

The effect of each reaction is governed by the hydroxyl-ion concentration and the temperature.

We have now studied the kinetics of the hydrolytic reaction catalyzed by hydrogen ions and correlated the resultant data with that obtained from the hydroxyl-ion catalysis. The pH for maximum stability to hydrolysis of sterile aqueous solutions of atropine and its salts has been calculated, as well as the influence of temperature.

HISTORICAL

The hydrolysis of atropine on heating either with HCl or Ba(OH)₂ solution was demonstrated by

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Kraut in 1864 (2) and others (3). Since then the deterioration of atropine in aqueous solution and the greater influence of alkalinity compared to acidity on this process seem to be generally recognized, although until recently (1) quantitative data have been lacking and there has been no agreement concerning the precise range of pH favorable to maximum stability. Stability and resistance to acid and alkali, up to pH 9.2, has been claimed for solutions of atropine salts as well as to heating at 100° for thirty minutes (4). Atropine nitrate and phosphate were found to be more stable in aqueous solutions than atropine sulfate (5). A 20% hydrolysis of atropine at pH 5 at 80° in five hours has been reported (6); on the other hand no appreciable decomposition was found on sterilization for twenty minutes at 120° until pH 6, or over, was reached, when hydrolysis became very rapid (7). The preservation of aqueous atropine solutions by buffering at pH 4-5 has been recommended (8). Stability is claimed for 0.1% sterilized atropine sulfate solution in storage if the pH is kept in the range 2.8-6.0 (9), distinct deterioration on storage occurring if the pH is kept at 7 or higher. An isotonic atropine-borax-boric acid solution deteriorated 44% in one month (10). A 0.1% solution of atropine sulfate in water was found to be stable for at least four months when stored in resistance glass, whereas in lime glass 90% deterioration occurred in three weeks (11). In addition to deterioration caused by chemical and physical factors instability of atropine in solution has been attributed to the presence of fungus contamination as the result of the complete loss of pharmacological activity in a three-day old atropine solution (12).

THEORETICAL

If (AtH^+) represents the concentration of the protonated form of atropine and k_{H^+} the catalytic constant of the hydrogen ion catalysis (13), then

$$-\frac{d(AtH^+)}{dt} = k_{H^+}(H^+)(AtH^+) \quad (\text{Eq. 1})$$

or,

$$-\frac{d \ln(AtH^+)}{dt} = k_{H^+}(H^+) \quad (\text{Eq. 2})$$

Since the right side of Eq. 2 is a constant at constant pH, the rate of hydrolysis will be kinetically of the first order with respect to drug concentration, with a velocity constant

$$k = k_{H^+}(H^+) \quad (\text{Eq. 3})$$

The most general expression for the observed velocity constant of reactions catalyzed by both hydrogen and hydroxyl ions (13) is

$$k = k_0 + k_{H^+}(H^+) + k_{OH^-}(OH^-) \quad (\text{Eq. 4})$$

where k_0 represents the velocity constant of the "spontaneous" reaction, i. e., catalysis by the solvent molecules, and for water solutions equals $k_{H_2O}(H_2O)$. Hydrolytic reactions catalyzed by both hydrogen and hydroxyl ions, with no detectable water reaction, include hydrolysis of carboxylic esters (13-15). The results reported by Bullock and Cannell (16) indicate this to be true for the hydrolysis of procaine. Assuming that the hydrolytic reactions of atropine

are included in this category and introducing the ionic product of water, $k_w = (OH^-)(H^+)$, Eq. 4, can be written

$$k + k_{H^+}(H^+) + k_{OH^-} \frac{K_w}{(H^+)} \quad (\text{Eq. 5})$$

Between the regions of high and low pH the velocity will pass through a minimum at a hydrogen ion concentration which is found by differentiating k with respect to (H^+) in Eq. 5 and equating to zero (17), thus

$$k_{H^+} - K_w \frac{k_{OH^-}}{(H^+)^2} = 0, \quad \text{or} \quad (H^+)_M = K_w \frac{k_{OH^-}}{k_{H^+}} \quad (\text{Eq. 6})$$

where $(H^+)_M$ is the hydrogen ion concentration at minimum velocity.

The value of k_M , the velocity constant at $(H^+)_M$, is obtained by substituting in Eq. 5 the value of $k_{OH^-}K_w$ from Eq. 6.

$$k_M = 2 k_{H^+}(H^+)_M \quad (\text{Eq. 7})$$

EXPERIMENTAL

Scope of the Studies.—The hydrolysis of atropine in perchloric acid solutions varying from 0.1 *N* to 0.4 *N* and at temperatures ranging from 70° to 90° was studied. The catalytic constant for the hydrogen ion catalyzed reaction was determined at the various temperatures and used to calculate the activation energy. With these values an equation was derived for predicting the rate of proton hydrolysis at any particular temperature and hydrogen ion concentration. By taking into account the effect of both hydroxyl and hydrogen ions the pH of minimum hydrolysis at various temperatures and the hydrolytic rates at these minimum pH values have been calculated. Also, the half lives of atropine solutions have been calculated for various pH values and temperatures.

Procedure.—A standardized solution of perchloric acid of the desired normality and containing 1 mg./ml. of atropine sulfate (U. S. P., twice recrystallized from ethanol; m. p. 189°-190° uncorr.) was kept at constant temperature in a thermostatically controlled bath. The hydrolytic reaction was followed by periodically removing 10-ml. samples for residual ester determination. The sample was made alkaline with ammonium hydroxide and the atropine base extracted with two 10-ml. portions of chloroform. The chloroform extracts were combined and extracted with exactly 10 ml. of 0.1 *N* HCl. The concentration of atropine in the acid solution was determined by ultraviolet absorption measurements at wavelengths 256.5 and 262 mμ using a Beckman model DU quartz spectrophotometer as previously described (1).

RESULTS

Influence of Ester Concentrations.—Velocity constants for atropine hydrolysis were determined in 0.099 *N*, 0.199 *N*, 0.301 *N*, and 0.401 *N* HClO₄ at 70.0°, 80.0° and 90.3°. Figures 1, 2, and 3 show that at constant temperature and hydrogen ion concentration the observed rate of hydrolysis of atropine

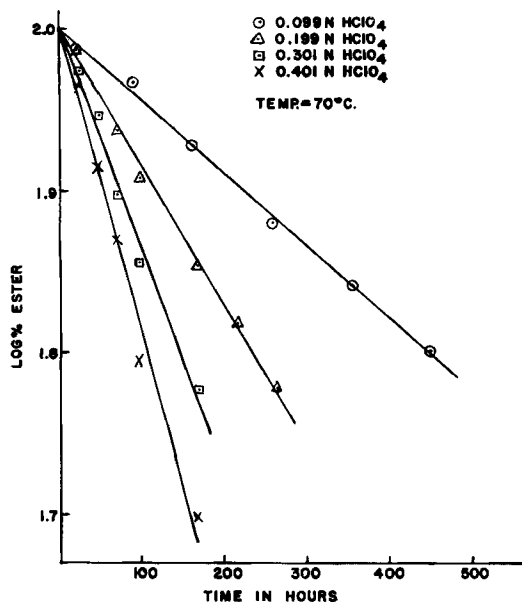


Fig. 1.—Hydrolysis of atropine in dilute perchloric acid solutions at 70°.

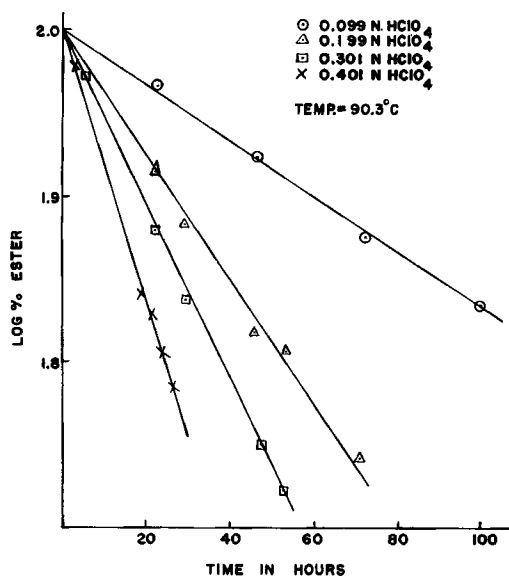


Fig. 3.—Hydrolysis of atropine in dilute perchloric acid solutions at 90.3°.

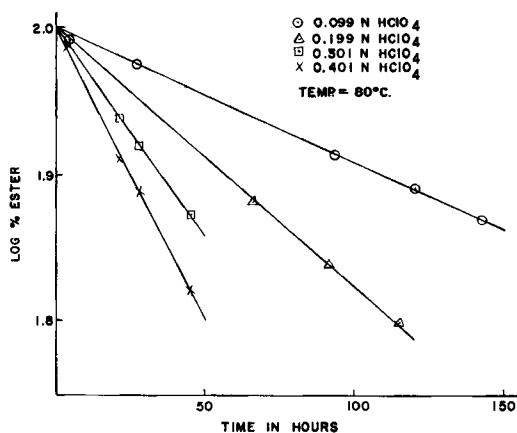


Fig. 2.—Hydrolysis of atropine in dilute perchloric acid solutions at 80°.

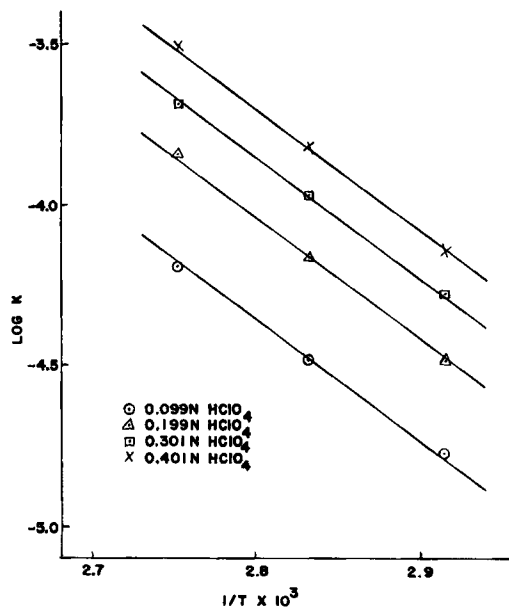


Fig. 4.—Temperature dependency of the hydrolytic reaction of atropine catalyzed by hydrogen ions. Log $K \text{ min.}^{-1}$ vs. reciprocal of the absolute temperature.

is first order with respect to ester concentration. These results are in accord with Eq. 3.

Influence of Hydrogen Ion Concentration and Temperature Dependency.—The regression line for the velocity constants obtained at the various normalities was calculated for each temperature (18). A straight line relationship was obtained, showing the dependency of the rate of hydrolysis on the hydrogen ion concentration. The slope of the line for each temperature is equal to the respective catalytic constant. The values obtained for this constant are: k_{H^+} @ 70° = $1.754 \times 10^{-4} \text{ min.}^{-1}$, k_{H^+} @ 80° = $3.668 \times 10^{-4} \text{ min.}^{-1}$, and k_{H^+} @ 90.3° = $7.350 \times 10^{-4} \text{ min.}^{-1}$.

In Fig. 4 the velocity constants are plotted against the reciprocal of the respective absolute temperatures. The straight line relationships indicate that

the mechanism responsible for the ester hydrolysis in acid solution is not altered with change in temperature. By subjecting the velocity constants to an analysis of covariance (18) the slope of the lines was found. The slope was set equal to $-E_a/2.303R$ and the energy of activation, E_a , was calculated to be $17,200 \pm 500$ calories per mole. By substituting both this value and the k_{H^+} at 70° in the Arrhenius

equation, $k = Ze^{-E_a/RT}$; or $\log k = \log Z - (E_a/2.303 RT)$, Z , the Arrhenius frequency factor, is found to be $1.54 \times 10^7 \text{ min.}^{-1}$, and

$k_{H^+} = 1.54 \times 10^7 e^{-17,200/RT} \text{ min.}^{-1}$ (Eq. 8)

By substituting this value for k_{H^+} into Eq. 3, the rate of hydrolysis of atropine due to proton catalysis can be calculated for any hydrogen ion concentration and temperature. The half lives of atropine determined experimentally are compared in Table I with values calculated from Eq. 3.

pH of Minimum Hydrolysis.—Equation 6 for the

TABLE I.—EXPERIMENTAL HALF LIVES OF ATROPINE COMPARED TO CALCULATED VALUES

Temp., °C.	N HClO ₄	Half Life, Hr.—	
		Exptl.	Calcd.
70.0	0.099	676	670
	0.199	352	333
	0.301	220	220
	0.401	161	166
80.0	0.099	329	328
	0.199	170	163
	0.301	107	108
	0.401	76	81
90.3	0.099	180	164
	0.199	80	81
	0.301	56	54
	0.401	37	40

TABLE II.—STABILITY OF ATROPINE AT pH OF MINIMUM HYDROLYSIS

Temp., °C.	pH, min.	<i>t</i> _{1/2} ^a Yr.
0	4.11	3.17 × 10 ⁴
10	3.97	7.50 × 10 ³
20	3.84	1.96 × 10 ³
30	3.74	5.87 × 10 ²
40	3.64	1.88 × 10 ²
50	3.54	6.34 × 10 ¹
60	3.46	2.36 × 10 ¹
70	3.39	9.42 × 10 ⁰
80	3.32	3.93 × 10 ⁰
90	3.28	1.82 × 10 ⁰
100	3.24	8.8 × 10 ⁻¹

^a *t*_{1/2} at the pH of minimum hydrolysis was calculated by means of the following equations:

$$\frac{1}{t_{1/2}} = \frac{2k_{H^+}(H^+)_M}{0.693}$$
$$2.886 (1.54 \times 10^7 e^{-17,200/RT} \text{ min.}^{-1}) (H^+)_M$$
$$- \log t_{1/2} = 7.6478 - \frac{3758.74}{T} + \log (H^+)_M$$

(H^+) of minimum hydrolysis of atropine may be written in log form, thus

$2 \log (H^+)_M = \log k_{OH^-} - \log k_{H^+} + \log K_w$ (Eq. 9)

On substituting into Eq. 9 the log of the value of k_{H^+} , given in Eq. 8, and for $\log k_{OH^-}$ the log of the the constant reported previously (1) for the singly charged (protonated) form, i. e., $2.10 \times 10^{10} e^{-12,700/RT}$, the equation may then be expressed as

$pH_M = \frac{1}{2} \left(pK_w - 3.13 - \frac{983}{T} \right)$ (Eq. 10)

The pH of minimum hydrolysis, Table II, changes inversely with increase in temperature, the values decreasing from 4.11 at 0° to 3.24 at 100°.

The half lives of solutions of atropine at various pH values and temperatures can be calculated for both hydroxyl-ion and hydrogen-ion catalysis. The former accounts for the instability above approximately pH 5 and the latter for instability below approximately pH 3. The half life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical. On the assumption that over this range of acidity instability of atropine is due to both hydroxyl ion and hydrogen ion catalyzed hydrolysis, and that the water reaction is minor, the half life at any pH value between these two regions and for any temperature can be calculated by means of the equation: $t_{1/2} = 0.693 / (k_{H^+} + k_{OH^-})$. The logarithmic form of this equation, after setting k_{H^+} equal to $0.693 / t_{1/2H^+}$ and k_{OH^-} equal to $0.693 / t_{1/2OH^-}$ and simplifying, is $\log t_{1/2} = \log t_{1/2H^+} + \log t_{1/2OH^-} - \log (t_{1/2H^+} + t_{1/2OH^-})$. Calculated half lives of solutions of atropine over the region of pH 2 to 7 at temperatures from 20 to 100° are given in Table III.

SUMMARY

The rate of acid hydrolysis of atropine has been measured in aqueous solution, and the activation energy and frequency factor calculated from Arrhenius plots. As expected, the hydrogen ion catalyzed hydrolysis of atropine is slow, the catalytic constant for the reaction at 40° having a value of $1.6 \times 10^{-5} \text{ min.}^{-1}$ compared to that for the hydroxyl ion catalysis of the protonated species of atropine of 33.6 min.^{-1} .

Above pH 4.5, the predominant catalytic reaction involves hydroxyl ion; below pH 3, the predominant catalytic reaction involves hydrogen ion; while

TABLE III.—PREDICTED STABILITY OF ATROPINE IN AQUEOUS SOLUTIONS *t*_{1/2} IN YEARS

Temp., °C.	pH						
	7.0	6.0	5.0	4.5	4.0	3.0	2.0
20	2.7	27	266	811	1800	548	56
30	0.61	6.1	61	194	473	203	21
40	0.16	1.6	16	49	135	80.7	8.5
50	..	0.44	4.4	13.8	39.2	33.3	3.6
60	..	0.14	1.4	4.3	12.9	14.4	1.6
70	..	..	0.46	1.39	4.34	6.52	0.76
80	..	..	0.17	0.5	1.63	3.04	0.37
90	..	..	..	0.21	0.65	1.48	0.19
100	..	..	..	0.1	0.31	0.76	0.10

between these two regions, both ions contribute to the hydrolysis.

The pH for maximum stability of atropine in sterile aqueous solution varies between 4.11 at 0° and 3.24 at 100°.

REFERENCES

- (1) Zvirblis, P., Socholitsky, I., and Kondritzer, A. A., *THIS JOURNAL*, **45**, 450(1956).
- (2) "Dispensatory of the United States of America," 25th ed., 1955, J. B. Lippincott Co., Philadelphia, Pa., Part I, pp. 124-127.
- (3) Manske, R. H. F., and Holmes, H. L., "The Alkaloids," Vol. I, Academic Press Inc., New York, 1950, p. 275.
- (4) Kuhl, G., *Arch. exptl. Path. Pharmacol.*, **109**, 295 (1925).
- (5) Bodnar, J., and Ferenczy, J., *Arch. Pharm.*, **263**, 566(1925).
- (6) Exler, Th., *Pharm. Weekblad*, **65**, 1152(1928).

- (7) Schou, S. A., and Bjerregaard, P. B., *Dansk. Tidsskr. Farm.*, **6**, 185(1932).
- (8) Vincke, B., and Delkers, H. A., *Med. Klin. (Munich)*, **33**, 80(1937).
- (9) Klyachkina, B. A., Guberman, P. F., and Lizgunova, M. V., *Farmatsiya*, No. 9-10, 19(1940).
- (10) Blok, C. J., *Pharm. J.*, **155**, 282(1945).
- (11) Ervenius, O., and Lindquist, H., *Farm. Revy.*, **45**, 577 (1946).
- (12) Simon, I., *Gazz. Ospedali Clin. (Milan)*, **36**, 17(1915), cited from ref. (2). See also *J. Am. Med. Assoc.*, **64**, 705 (1915), and *C. A.*, **9**, 953³(1915).
- (13) Bell, R. P., "Acid-Base Catalysis," Oxford University Press, 1941.
- (14) Bell, R. P., "Advances in Catalysis," Vol. IV, Academic Press, Inc., New York, 1952.
- (15) Kilpatrick, M., "Advances in Catalysis," Vol. VI, Academic Press, Inc., New York, 1954.
- (16) Bullock, K., and Cannell, J. S., *Quart. J. Pharm. and Pharmacol.*, **14**, 241(1941).
- (17) Glasstone, S., "Textbook of Physical Chemistry," 2nd ed., U. Van Nostrand Co., Inc., 1946, p. 1135.
- (18) Snedecor, G. W., "Statistical Methods," 4th ed., The Iowa State College Press, Ames, Iowa, 1946, chap. 6.

Enzymatic Decomposition of Digitalis Glycosides*

By OLE GISVOLD† and S. E. WRIGHT‡

Using paper chromatographic methods the glycosidic constituents of freshly gathered leaves of *Digitalis lanata* have been examined before and after exposure to a limited period of enzymatic action. It appears that the original plant does not contain desglucoglycosides in quantities detectable by very sensitive methods, but that after exposure to enzyme degradation under defined conditions, glucose only is removed from the lanatosides to give acetyl digoxin, acetyl digitoxin, and probably acetyl gitoxin. The separation and identification of the less water soluble digitalis glycosides, some of their acetyl derivatives, and their genins, has been helped by the use of a new temperature-insensitive method of paper chromatography.

THE NUMBER of cardiac glycosides isolated from or detected in species of *Digitalis* continues to increase. Using paper chromatographic methods, several workers have detected apparently new glycosides in extracts of the leaves of *D. lanata* and *D. purpurea*. Jensen (1) detected nine unknown substances in an aqueous extract of *D. purpurea*. Sasakawa (2) revealed six substances which fluoresced similarly to the B series of digitalis glycosides, but the method used for extraction was not described. Aldrich, Frith, and Wright (3) used an enzyme-inhibiting, extraction process based on that used by Stoll and Kreis (4) in the isolation of the "genuine" glycosides lanatosides A, B, and C, and showed the presence of six substances, some of which were apparently cardioactive, in very young and mature plants of *D. lanata*.

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Several new glycosides isolated from *D. lanata* and *D. purpurea* have been described in recent years, and the literature has been reviewed by Jensen (1) and by Tamm (5). In addition, we could mention gitaloxin (16 formyl gitoxin), verodoxin (16 formyl strosipeside), and odoroside H (desgluco digitalinum verum), which have been reported by Haack, Kaiser, Gube, and Spingler (6) to be constituents of the "gitalin" fraction obtained from *D. purpurea*. Odoroside A also was detected in small quantities in *D. lanata* (7). Tschesche and co-workers (8) have isolated cardio-inactive compounds, resembling the digitalis glycosides in some of their chemical properties, from *D. lanata* and *D. purpurea* (digifolein) and from *D. purpurea* (digipurpurin). Murphy (9) found diginatin, the tentative structure of which is 16-hydroxy digoxin, occurring in small quantities with digoxin obtained from *D. lanata*. The same author (10) has also described another glycoside from *D. lanata*, gitoside, as the monodigitoxoside of gitoxigenin.

Since the work of Stoll and Kreis (4), it has been realized that many of the glycosides isolated from digitalis are artifacts produced during the