

nificant percentages were located at the other positions.

The label at position 2 could result from the direct polymerization of unbroken 6-carbon chains from D-glucose-2-C<sup>14</sup>. However, the presence of label at other positions shows that much of the labeled cellulose was formed from breakdown products, and, indeed, label in the two position could also have been obtained in this manner.

The mechanism that caused the distribution of label and the comparatively low specific radioactivity in the cellulose are at present unknown. These results, as well as other data reported,<sup>3</sup> suggest

that random scissioning of the D-glucose and its degradation products could account for the asymmetrical distribution of label found. Only further investigation, such as a detailed study of the metabolic intermediates, will permit the formation of more definitive conclusions regarding the mechanism of the cellulose biosynthesis.

**Acknowledgment.**—The authors are grateful to Dr. H. S. Isbell, National Bureau of Standards, Washington, D. C., for the supply of D-glucose-2-C<sup>14</sup> used in this investigation.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

## Alkaline Hydrolysis of Scopolamine Methyl Bromide and Other Esters of Quaternary Amino Alcohols<sup>1</sup>

BY ROBERT BRUCE MOFFETT AND EDWARD R. GARRETT

RECEIVED AUGUST 23, 1954

Esters of quaternary amino alcohols have been found to hydrolyze in alkali much more rapidly than the corresponding esters of tertiary-amino alcohols. The rate constants for the hydrolysis of several of these esters were determined. Scopolamine is known to rearrange on hydrolysis giving the basic moiety scopoline. However it was found that scopolamine methyl bromide hydrolyzes without rearrangement to scopoline methyl bromide.

A study of the applicability of the acidic dye colorimetric method<sup>2</sup> to the assay of scopolamine methyl bromide<sup>3</sup> (I) indicated that this salt is quite unstable in dilute alkaline solutions.<sup>4</sup> Preliminary titrations showed that this instability was due to extremely rapid hydrolysis of the ester. Only one equivalent of base was consumed and the acid liberated had a  $pK'_a$  value which checked with that of tropic acid. There was no evidence of destruction of the quaternary salt. In order to put this study on a more quantitative basis, the rates of hydrolysis were determined for a number of esters of amino alcohols and their corresponding quaternary salts.

Since, even in very dilute alkali, many of these esters hydrolyzed too rapidly for titration of aliquots, an automatic electrometric titrator was used. Samples of the esters in one equivalent of 0.025 *N* alkali were placed in this instrument which can record  $pH$  as a function of time. From such curves values for the reciprocal of the hydroxyl ion concentration were obtained. Plotting these against time gave typical bimolecular rate curves (Fig. 1). The rates for the slower hydrolyzing esters were obtained by mixing the ester with one equivalent of standard alkali and titrating aliquots from time to time. The curves in Fig. 2 and the bottom two in Fig. 1 were obtained by this latter method. It will be noted that the time in Fig. 1 is in minutes while that in Fig. 2 is in hours. Also the two bottom curves of Fig. 1 are repeated as the two top curves

of Fig. 2. From these data the bimolecular rate constants (Table I) were calculated.

TABLE I  
BIMOLECULAR RATE CONSTANTS<sup>a</sup>

No. (Figs. 1 and 2)	Name of compound	$k^a$
1	$\beta$ -Diethylaminoethyl xanthine-9-carboxylate methyl bromide <sup>b</sup>	>100
2	Scopolamine methyl bromide <sup>b</sup>	28
3	Atropine methyl bromide	14
4	2-(2,5-Dimethyl-1-pyrrolidyl)-ethyl phenyl- $\Delta^2$ -cyclohexenylacetate methyl bromide <sup>b</sup>	3.1
5	Acetylcholine chloride	2.1
6	Scopolamine hydrobromide	0.27
7	2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl cyclopentyl- <i>n</i> -propylacetate methyl bromide <sup>b</sup>	0.1
8	Atropine	0.08
9	2-(2,5-Dimethyl-1-pyrrolidyl)-ethyl phenyl- $\Delta^2$ -cyclohexenylacetate hydrochloride <sup>c</sup>	0.005
10	2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl cyclopentyl- <i>n</i> -propylacetate hydrochloride <sup>c</sup>	<0.001

<sup>a</sup>  $k$  (1./mole min.) in 48% ethanol as determined by hydrolysis of 0.025 *M* solutions of esters in 0.025 *N* NaOH at 25°. <sup>b</sup> Reported before the Division of Medicinal Chemistry, A.C.S. at Los Angeles, California, March, 1953, Abstracts, p. 8L. <sup>c</sup> R. B. Moffett and J. H. Hunter, THIS JOURNAL, 74, 1710 (1952).

(1) Presented before the Division of Medicinal Chemistry, A.C.S. of Kansas City, Missouri, March, 1954, Abstracts, p. 19M.

(2) F. Durick, J. S. King, P. A. Ware and G. Cronheim, *J. Am. Pharm. Assoc.*, 39, 680 (1950).

(3) Pamine bromide, The Upjohn Company brand of methscopolamine bromide.

(4) Private communication from Dr. Wm. L. Miller, of our Department of Pharmacology, Mr. Wm. A. Struck and Miss Eleanor J. Scott, of our Analytical Chemistry Laboratory.

Although there is a great variation in the rates of hydrolysis of these esters it will be noted that in all cases the methyl bromide quaternary salts hy-

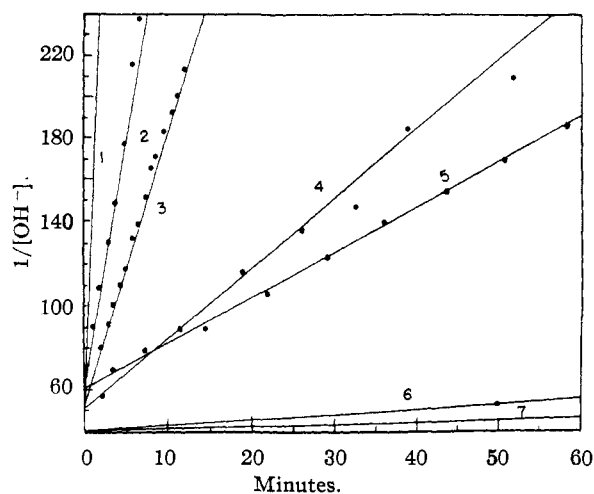


Fig. 1.—Bimolecular rate plots (numbers refer to compounds listed in Table I).

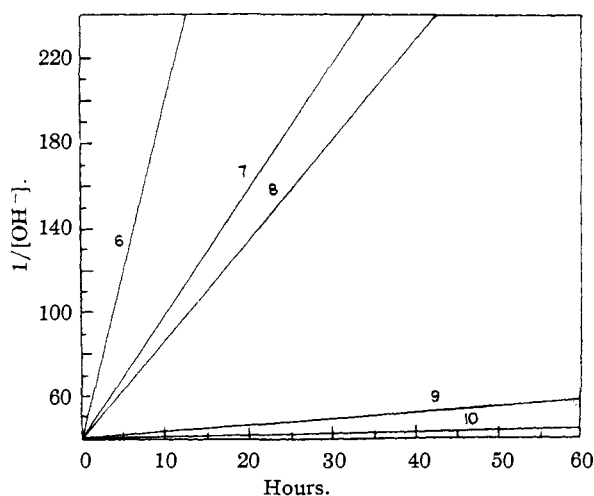


Fig. 2.—Bimolecular rate plots (numbers refer to compounds listed in Table I).

drolyzed at least one hundred times as fast as the corresponding tertiary amines.

One quaternary amino ester,  $\beta$ -diethylaminoethyl xanthene-9-carboxylate methyl bromide,<sup>5</sup> hydrolyzed too rapidly for the electrometric titrator to record the rate, and one ester, 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl cyclopentyl-*n*-propylacetate, hydrolyzed too slowly for practical measurement in the concentration of alkali (0.025 *N*) used. Consequently the curves for these compounds, Figs. 1 and 2, and the rates in Table I are minimum and maximum estimates.

Although scopolamine methyl bromide (I) is very rapidly hydrolyzed in alkali it is stable for many months in water and even in 0.1 *N* hydrochloric acid.

It is evident that there are many factors influencing the hydrolysis of esters of amino alcohols. However since basic hydrolysis is generally assumed to take place through hydroxyl ion attack on the ester, it would be expected that the permanent positive charge on the quaternary salts would attract

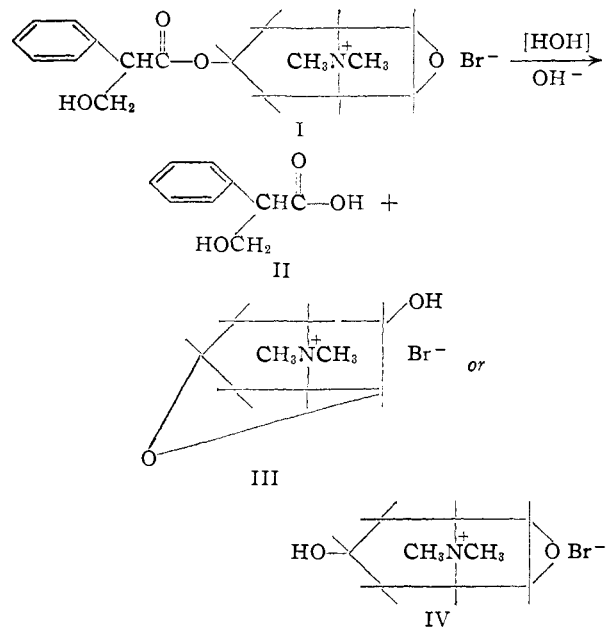
(5) *Banthine bromide*, G. D. Searle and Company.

hydroxyl ions and thus facilitate the hydrolysis. Conversely the hydrogen ion attack of acid hydrolysis would be hindered by the repulsion of the hydrogen ions by the positive charge.

The hydrolysis of the alkaloid scopolamine, under either alkaline or acid conditions, is known<sup>6</sup> to yield (besides tropic acid (II)) only the rearrangement product scopoline.

The true basic moiety of scopolamine, scopine, has only been obtained by very slow hydrolysis in a carefully buffered solution of ammonium hydroxide and ammonium chloride.<sup>7</sup>

It was thought likely that the alkaline hydrolysis of scopolamine methyl bromide (I) would also yield the rearranged product, namely, scopoline methyl bromide (III). When scopolamine methyl bromide (I) was hydrolyzed with sodium hydroxide difficulties were encountered in the separation of the quaternary salt from the sodium salts and therefore barium hydroxide was used which could be removed as a sulfate prior to isolation of the quaternary salt. In this way 1-tropic acid (III) and a nicely crystalline quaternary bromide were obtained in good yield which gave the same analysis and melting point as scopoline methyl bromide (III), prepared from authentic scopoline. Moreover a mixed melting point gave no depression. However, the crystal shape of this salt (needles) was different from that of scopoline methyl bromide (III) (cubes) even when the two salts were recrystallized from the same solvent and seeded with the same sample of scopoline methyl bromide. Furthermore, the infrared spectra<sup>8</sup> showed that the two salts were definitely different even though the same functional groups were indicated. Although both salts



(6) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 303.

(7) R. Willstätter and E. Berner, *Ber.*, **56**, 1079 (1923).

(8) Infrared spectra are by Dr. James L. Johnson and associates, of our Department of Physics, using an instrument equipped with a sodium chloride prism. The stronger characteristic bands measured on a mineral oil suspension of the compound are given in the experimental part.

are quite stable at room temperature it was found that the hydrolysis product could be converted to scopoline methyl bromide (III) by heating the solid above 200°. All this evidence seemed to indicate that scopolamine methyl bromide (I) is hydrolyzed to the unrearranged scopine methyl bromide (IV). That this is indeed the case was confirmed by converting authentic scopine prepared as described by Willstätter and Berner,<sup>7</sup> to its methyl bromide quaternary salt, which was found to be identical in all respects with the hydrolysis product of scopolamine methyl bromide.

### Experimental<sup>9,10</sup>

**Determination of Rate Constants of Fast Hydrolyzing Esters.**—A 0.05 *M* solution of the ester of a quaternary amino alcohol in 95% ethanol was placed in the cell of a Precision Dow Recordomatic Titrator equipped with a Beckman Type E glass electrode and a saturated calomel electrode. The solution was kept at 25 ± 2° and purged by bubbling in decarbonated nitrogen throughout the experiment. An equal volume of 0.05 *N* aqueous sodium hydroxide solution was added, making the final 48% ethanol solution 0.025 *M* in both alkali and ester. The observable pH was automatically recorded on a chart which moved at a definite rate. Blanks were run with solutions of alkali at several concentrations up to 0.025 *M* in 48% ethanol in order to prepare a standard curve for this machine and these electrodes. Using this curve the hydroxyl ion concentration of the hydrolyzing solution was determined at various times. Plots of the reciprocal of these hydroxyl ion concentrations against time for each ester are given in Fig. 1.  $\beta$ -Diethylaminoethyl xanthine-9-carboxylate methyl bromide saponified so fast that the electrodes could not even record the change. There is a time lag in electrode equilibration and this rate of equilibration is the minimum possible rate of hydrolysis of this ester. The curve in Fig. 1 and the rate constant in Table I for this compound are thus only minimum estimates. 2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl cyclopentyl-*n*-propylacetate methyl bromide and all the tertiary amino esters hydrolyzed too slowly for proper application of this technique and were therefore studied by the following method.

**Determination of Rate Constants for More Slowly Hydrolyzing Esters.**—Solutions of the esters in standard alkali were made up as above and kept at 25 ± 2°. The concentrations were 0.025 *M* in ester and alkali in 48% ethanol except in the case of 2-(2,5-dimethyl-1-pyrrolidyl)-ethyl phenyl- $\Delta^2$ -cyclohexenylacetate hydrochloride which was 0.0286 *M* in sodium hydroxide and 0.0143 *M* in ester in 54% ethanol. Where hydrochloride or hydrobromide salts were used an extra equivalent of alkali was added to liberate the free base. At intervals aliquots were removed and titrated with the electrometric titrator. Except with 2-(2,5-dimethyl-1-pyrrolidyl)-ethyl phenyl- $\Delta^2$ -cyclohexenylacetate hydrochloride the rate constants were determined from the slope of the plot of the reciprocal of the hydroxyl ion concentration against time. In the latter case the equation for bimolecular reaction rate was used. 2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl cyclopentyl-*n*-propylacetate hydrochloride showed no significant alkali consumption (except that needed to neutralize the HCl) in three days.

Scopolamine methyl bromide (I) showed no reaction beyond 1:1 stoichiometry with sodium hydroxide in 0.03 *M* solutions of the ester and 0.04 *N* alkali at 30° in water. A 0.025 *M* solution of scopolamine methyl bromide in 0.1 *N* hydrochloric acid showed no change in titration even after standing at 25° for three months. Solutions of this quaternary salt in water have also showed no change after standing at room temperature for several months or for over a year in solutions buffered slightly acid.

**Scopine Methyl Bromide (IV) and 1-Tropic Acid (II) by the Hydrolysis of Scopolamine Methyl Bromide (I).**—To a solution of 85.5 g. (0.5 mole) of barium hydroxide in 2.2 l.

of water was added 200 g. (0.5 mole) of scopolamine methyl bromide (I) (Pamine bromide). After standing at room temperature for 35 minutes, the solution was acidified to about pH 2 with cold dilute H<sub>2</sub>SO<sub>4</sub> (about 28 ml. of concentrated H<sub>2</sub>SO<sub>4</sub> mixed with ice was used). The resulting suspension of BaSO<sub>4</sub> was extracted five times with ether (total volume about 1.5 l.). The ether solution was washed with water and then with saturated NaCl and dried over Na<sub>2</sub>SO<sub>4</sub>. On standing in the refrigerator the ether solution deposited crystals mixed with the Na<sub>2</sub>SO<sub>4</sub>. The mixture was filtered and the crystallized 1-tropic acid (II) was extracted from the Na<sub>2</sub>SO<sub>4</sub> with absolute methanol. The methanol and ether solutions were combined, distilled to dryness under reduced pressure below 55°. Benzene was added and removed under reduced pressure leaving a crystalline residue which was dissolved in boiling ethyl acetate, filtered and cooled in the refrigerator. The resulting crystals of 1-tropic acid (II) were collected, washed with ethyl acetate and dried, m.p. 129–130°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> -75° (0.652% in H<sub>2</sub>O), yield 40.6 g. (49%). On allowing the filtrate to evaporate an additional yield of tropic acid was obtained.

The aqueous suspension of BaSO<sub>4</sub> was treated with BaBr<sub>2</sub> solution until the excess H<sub>2</sub>SO<sub>4</sub> was just completely precipitated. The mixture was filtered with Super-cel and the filtrate was distilled to dryness under reduced pressure below 45°. Methanol was added and removed by distillation under reduced pressure. The residue was recrystallized from about 300 ml. of methanol giving colorless needles which were collected, washed with methanol, absolute ethanol, and absolute ether; weight 91.3 g., m.p. about 295.5–296° dec. (after sintering slightly at about 240° and darkening from about 250°).<sup>11</sup> By diluting the methanol filtrate with ether and recrystallizing the resulting precipitate from methanol an additional yield of 21.1 g. of only slightly less pure material was obtained; total yield 112.4 g. (90%). A sample of this second crop was recrystallized from absolute ethanol giving nicely crystalline material with essentially the same decomposition point. The infrared spectra of these fractions were identical and the same as that described below except for an extra band at 1100 cm.<sup>-1</sup> which may be due to solvent or slight impurity.

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>BrNO<sub>2</sub>: C, 43.21; H, 6.45; Br, 31.95. Found: C, 43.57; H, 6.18; Br, 31.36.

In another run using 11.95 g. (0.03 mole) of scopolamine methyl bromide the barium was precipitated with CO<sub>2</sub> instead of H<sub>2</sub>SO<sub>4</sub> and the solution was acidified with HBr. A yield of 4.03 g. (80.8%) of 1-tropic acid (II), m.p. 123–126°, was obtained which after recrystallization from ethyl acetate gave 2.82 g. of crystals, m.p. 128.5–130°, [ $\alpha$ ]<sub>D</sub><sup>20</sup> -73° (0.948% in H<sub>2</sub>O). The first crop of scopine methyl bromide (IV) crystallized from methanol and then from absolute ethanol (containing a little methanol) gave 2.27 g. of crystals, m.p. 297–299° dec. (darkening from about 245°).<sup>11</sup> A sample was recrystallized carefully from absolute ethanol giving nicely crystalline needles, m.p. 294–297° dec. (after sintering slightly at 235° and darkening from about 235–240°).<sup>11</sup> Its infrared absorption spectrum<sup>8</sup> showed bands at 1187, 1015, 990, 939, 870 and 851 cm.<sup>-1</sup>.

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>BrNO<sub>2</sub>: C, 43.21; H, 6.45; Br, 31.95; N, 5.60. Found: C, 43.54; H, 6.25; Br, 31.83; N, 6.00.

**Scopoline Methyl Bromide.<sup>12</sup>**—To an aqueous solution of 5 g. (0.023 mole) of scopoline nitrate<sup>13</sup> was added 25 ml. (0.046 mole) of a 20% solution of sodium carbonate. The free base remained in solution but was separated by continuous extraction with benzene. The benzene solution was cooled to about 5° and a large excess of cold methyl bromide was added. The stopper was clamped in the flask and it was allowed to stand at room temperature for one week. The crystalline product was collected and recrystallized from absolute ethanol. Samples allowed to slowly crystallize from either absolute ethanol or methanol separated in cubic shaped crystals, m.p. 297–298° dec. (darkening from about 275°).<sup>11</sup> A mixed melting point between this and the above scopolamine hydrolysis product gave no depression; however, the infrared spectrum<sup>8</sup> definitely

(11) Melting point taken in capillary tube heated in a liquid bath.

(12) This compound was prepared by Mr. Brooke D. Aspergren in These Laboratories.

(13) Scopoline Nitrate was obtained from S. B. Penick and Company.

(9) Elemental analyses and optical rotations are by Mr. Wm. A. Struck and associates, in our Analytical Chemistry Laboratory.

(10) We gratefully acknowledge the technical assistance of Miss K. G. Stimson in the rate studies.

showed that they were different, giving bands at 3180, 1106, 1032, 988, 950, 925, 888 and 865  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_9\text{H}_{16}\text{BrNO}_2$ : C, 43.21; H, 6.45; Br, 31.95; N, 5.60. Found: C, 43.41; H, 6.53; Br, 31.86; N, 5.42.

**Scopoline Methyl Bromide (III) by Rearrangement of the Scopolamine Hydrolysis Product.**—A 0.1-g. sample of crystalline scopoline methyl bromide was heated under nitrogen in an oil-bath at 225–244° for one hour. The slightly darkened crystalline residue was recrystallized from 5 ml. of absolute ethanol giving typical cubic shaped crystals, m.p. 297–299° dec.<sup>11</sup> The infrared spectrum<sup>8</sup> showed this to be identical with scopoline methyl bromide (III).

This ability to rearrange without melting doubtless explains the lack of depression in the mixed melting point between scopoline methyl bromide and scopine methyl bromide.

**Scopine Methyl Bromide (IV) from Scopine.**—Scopine was prepared by the hydrolysis of scopolamine with an

ammonium chloride–ammonium hydroxide buffered solution as described by Willstätter and Berner.<sup>7</sup> Nicely crystalline material was obtained, m.p. 75.5–77° in a capillary tube heated in a liquid bath; and m.p. 82–82.5° on a Fisher-Johns melting point block.<sup>14</sup>

A solution of 0.5 g. (0.0032 mole) of this scopine in 5 ml. of absolute ethanol was cooled to 0° and about 2 ml. of cold methyl bromide was added. The stopper was clamped in the flask and it was allowed to stand at room temperature. Within a half-hour crystals had started to separate and after 22 hours the product was collected, washed with absolute ethanol and absolute ether and dried giving 0.73 g. (90%) of nicely crystalline needles, m.p. 295–295.5° dec. (with darkening from about 230°).<sup>11</sup> The infrared spectrum<sup>8</sup> was identical with that of the above scopolamine methyl bromide hydrolysis product.

(14) Willstätter and Berner<sup>7</sup> report a m.p. 79° (cor.).

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE]

### Alkaloids of the Amaryllidaceae. III. Isolation of Five New Alkaloids from *Haemanthus* Species<sup>1</sup>

BY W. C. WILDMAN AND CAROL J. KAUFMAN

RECEIVED SEPTEMBER 3, 1954

The alkaloid content of ten identified and three unidentified species of *Haemanthus* has been investigated. Five new alkaloids named coccinine, manthidine, manthine, montanine and natalensine have been isolated and characterized. Tazettine was the major alkaloid found in *H. albiflos* and lycorine was isolated in trace amount from *H. coccineus*.

The plant genus *Haemanthus*, which is native to South Africa, has been known for many years to possess physiological activity. Nearly fifty years ago, Juritz<sup>2</sup> reported on the toxicity of several *Haemanthus* species. The native Africans have employed extracts of *Haemanthus* and the closely related *Boophone* (earlier spelling *Buphane*) as topical treatment of such diverse afflictions as leprosy, ulcers, febrile colds, asthma, coughs and wounds.<sup>3,4</sup>

While no work has been reported<sup>4a</sup> since that of Juritz on the alkaloids of *Haemanthus*, the alkaloids of *Boophone disticha* Herb. (*Haemanthus toxicarius* Herb.) have been investigated more completely. Tutin<sup>5</sup> isolated buphanine, lycorine and two amorphous bases from this source. Lewin<sup>6</sup> found the amorphous base haemanthine in the same plant. This early work has been extended and strengthened by Cooke and Warren<sup>7</sup> who have

verified the existence of haemanthine and revised its molecular formula to  $\text{C}_{18}\text{H}_{28}\text{NO}_6$ .<sup>8</sup> Recently a new amorphous alkaloid, distichine,  $\text{C}_{19}\text{H}_{23}\text{NO}_4$ , has been isolated from *B. disticha*.<sup>8</sup>

This paper reports a study of the crystalline alkaloids found in nine species of *Haemanthus*. *H. puniceus* (N-951) was received in this country in 1951 and cultivated at the U. S. Plant Introduction Garden, Glenn Dale, Maryland, until April, 1954, when it was sent to this Laboratory for processing. The bulbs of *H. albiflos* were of South African origin, purchased in 1938 from nurseries in Haarlem, Netherlands, and propagated in Maryland until April, 1954. The remaining specimens were gathered in South Africa during the period from December, 1952, through February, 1953, and processed shortly after arrival in this country. Approximately thirty grams of each species was examined first for the presence of alkaloids by precipitation tests with silicotungstic acid and Mayer reagent. Those bulbs which gave negative or very weakly positive tests were not studied further. The bulbs which gave positive reactions were processed according to a standard procedure outlined in the previous paper.<sup>1b</sup>

With the exception of *H. natalensis*, which was much richer in alkaloidal material, the alkaloid fractions appear to represent between 0.1 and 0.6% of the total bulb weight. The absence of alkaloids in the sample of *H. magnificus* was surprising since all other species of *Haemanthus* contained alkaloidal material. It is of interest to note that *H. amarylloides*, *H. coccineus* and the unidentified species N-47 and N-50, all of which possessed nearly the same amount of basic material, contained the same major alkaloids.

(1) Papers I and II of this series: (a) W. C. Wildman and W. T. Norton, *THIS JOURNAL*, **76**, 152 (1954); (b) W. C. Wildman and C. J. Kaufman, *ibid.*, **76**, 5815 (1954).

(2) C. F. Juritz, *S. African J. Sci.*, **8**, 98 (1911); *ibid.*, **11**, 116 (1921); *Rept. Senior Analyst*, Cape of Good Hope, **G-43**, 40 (1906).

(3) T. S. Githens, "Drug Plants of Africa," The University of Pennsylvania Press, The University Museum, Philadelphia, Penna., 1949, pp. 33, 91.

(4) J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern Africa," E. and S. Livingston, Edinburgh, 1932, p. 25.

(4a) Since this paper was submitted, papers by H.-G. Boit [*Chem. Ber.*, **87**, 1339, 1448 (1954)] have appeared on alkaloids of the *Haemanthus* genus. From the *Haemanthus* hybrid "King Albert," he obtained lycorine, "haemanthamine," and "haemanthidine." Actual comparison has not been effected, but it is obvious that "haemanthamine" and "haemanthidine" are identical with our natalensine and the alkaloid of m.p. 190–192° from *H. puniceus*, respectively. We have found that the alkaloid of m.p. 188–194° from *H. albiflos* is impure lycorenine which is identical in its infrared spectrum with an authentic sample of lycorenine kindly furnished by Prof. S. Uyeo. Lycorenine and tazettine were isolated by Boit from *H. albiflos*.

(5) F. Tutin, *J. Chem. Soc.*, **99**, 1240 (1911).

(6) L. Lewin, *Arch. expil. Path. Pharmacol.*, **68**, 333 (1912).

(7) J. Cooke and F. Warren, *J. S. African Chem. Inst.*, **6**, 2 (1953).

(8) F. L. Warren, *J. Chem. Soc.*, submitted for publication.