lized as colorless thin needles. It was extracted with chloroform; the chloroform solution was washed with aqueous bicarbonate solution followed by water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crude solid product showed one major spot and at least three other minor spots of varying intensities. The mixture was separated by preparative tlc; work-up of the major band gave 58 mg of crude ketone **8**, which showed a melting point range of 198–204° after one crystallization from acetone–isopropyl ether. Four more recrystallizations from the same solvent system raised the melting point to 214–217°. The product showed a single spot in tlc; $[\alpha]^{24}D$ +52.84° (*c* 1.19); λ_{max} 210 mμ (ε 7200); ir bands at 1760, 1708, 1668, 1450, 990, 950, and 880 cm^{-1}.

Registry No.—**2a**, 17322-81-5; **2b**, 17230-63-6; **3**, 17230-64-7; **4**, 17322-82-6; **5**, 17230-66-9; 2,4-dinitrophenylhydrazone of **5**, 17230-67-0; **6**, 17230-68-1; **8**, 17230-69-2; **9a**, 17230-70-5; **9b**, 17230-71-6; **10**, 17322-83-7.

Novel Alkaloids Containing the [2]Benzopyrano[3,4-*c*]indole Nucleus[1-3]

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Received April 15, 1968

Five new Amaryllidaceae alkaloids containing the [2]benzopyrano[3,4-*c*]indole nucleus have been isolated, and their structures were established. The structures and stereochemistry of haemanthidine (**5a**) and macronine (**4b**) are completely defined. Evidence is presented that tazettine (**1a**, R = H) and criwelline (**1b**, R = H) may be rearrangement artifacts.

Although the total number of Amaryllidaceae alkaloids is close to 150, only three alkaloids have been found to contain the [2]benzopyrano[3,4-*c*]indole nucleus. Tazettine is one of the most abundant alkaloids of this family.[4,5] Structural studies on this base began in 1934[6] and culminated in the assignment of structure (**1a**, R = H) in 1966.[7] Criwelline (**1b**, R = H), the C_3 epimer of tazettine, was first isolated from *Crinum powellii* Hort. var. *album* in 1956.[8] It was related structurally to 6-hydroxycrinamine (**5b**) and tazettine in 1959.[9] Macronine was isolated in 1964 from *Crinum macrantherum* Engl., and its functional groups were determined.[10] In the same year it was assigned structure **4b**,[11] but the stereochemistry at C_{6a} was not defined.

The advent of thin and thick layer chromatography has made possible the isolation of pure material from mixtures which were previously inseparable. Using this powerful technique, several Amaryllidaceae species have been reinvestigated to study other alkaloids that have escaped previous detection.

Alkaloid Isolation from *Sprekelia formosissima* L. (Herb.) and *Ismene calithina* (Nichols).—Tazettine, haemanthamine, haemanthidine, and ismine have been reported to occur in *Sprekelia formosissima*.[12,13] In a recent reexamination of the alkaloids in this plant, using procedures which avoided strongly basic conditions (including chromatography on alumina), the alkaloid fraction appeared devoid of tazettine by tlc criteria. *Ismene calithina*, reported to contain galanthamine, homolycorine, lycorine, nerinine, and tazettine,[14] when processed under similar conditions, was also found by tlc to contain no tazettine.

The major alkaloid in each case was identified as pretazettine ($C_{18}H_{21}NO_5$). Although the base defied crystallization, crystalline hydrochloride and hydrobromide salts have been obtained. Pretazettine is converted readily into tazettine under a variety of basic conditions. Chromatography on basic alumina or treatment with 0.1 *N* sodium hydroxide at 25° for 1 hr affords a quantitative conversion into tazettine. Pretazettine is unstable as the free base in solution and gradually rearranges to tazettine upon standing. An aqueous solution of pretazettine is converted at 70° into tazettine in less than 1 hr. Under dilute acidic conditions, however, pretazettine appears to be stable. This facile rearrangement suggests that the true alkaloid in the plant is pretazettine. The tazettine isolated by previous workers probably arises from this rearrangement which has occurred during routine alkaloid isolation conditions.[15]

The chemical and physical properties of pretazettine (as well as its salts) are in good agreement with those reported by Proskurnina[16] for isotazettine, although a direct comparison has not been possible. The name isotazettine should not be continued because it introduces confusion with the existing references to isotazettine (criwelline), tazettinol, and isotazettinol. These are all C_{6a} hydroxy derivatives of the [2]benzopyrano[3,4-*c*]indole nucleus but vary in stereochemistry of the substituent at C_3.

Comparison of the ir and nmr spectra of tazettine and pretazettine indicates that the bases have many structural features in common. A difference between

(1) Supported by a grant, HE 7503, from the National Institutes of Health.

(2) For the preliminary communication, see W. C. Wildman and D. T. Bailey, *J. Amer. Chem. Soc.*, **89**, 5514 (1967). Subsequent to our initial communication, comparable results have been reported by W. Döpke and P. W. Jeffs, *Tetrahedron Lett.*, 1307 (1968).

(3) Taken from the dissertation of D. T. Bailey submitted in partial fulfillment of the requirements for the Ph.D. degree, Iowa State University, 1968.

(4) W. C. Wildman, *Alkaloids*, **6**, 372 (1960).

(5) H.-G. Boit. "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, p 410.

(6) E. Späth and L. Kahovec, *Ber.*, **67**, 1501 (1934).

(7) (a) R. J. Highet and P. F. Highet, *Tetrahedron Lett.*, 4099 (1966). Other papers on the structure of tazettine are (b) W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 2962 (1955); (c) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *ibid.*, 4749 (1956); (d) T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *Chem. Ind.* (London), 1088 (1955); (e) T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *ibid.*, 411 (1956); (f) R. J. Highet and W. C. Wildman, *ibid.*, 1159 (1955); (g) H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959); (h) Y. Tsuda and S. Uyeo, *ibid.*, 2485 (1961); and (i) R. D. Haugwitz, P. W. Jeffs, and E. Wenkert, *ibid.*, 2001 (1965).

(8) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956).

(9) H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959).

(10) H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **47**, 185 (1964).

(11) C. F. Murphy and W. C. Wildman, *Tetrahedron Lett.*, 3857 (1964).

(12) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955).

(13) R. J. Highet, *J. Org. Chem.*, **26**, 4767 (1961).

(14) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).

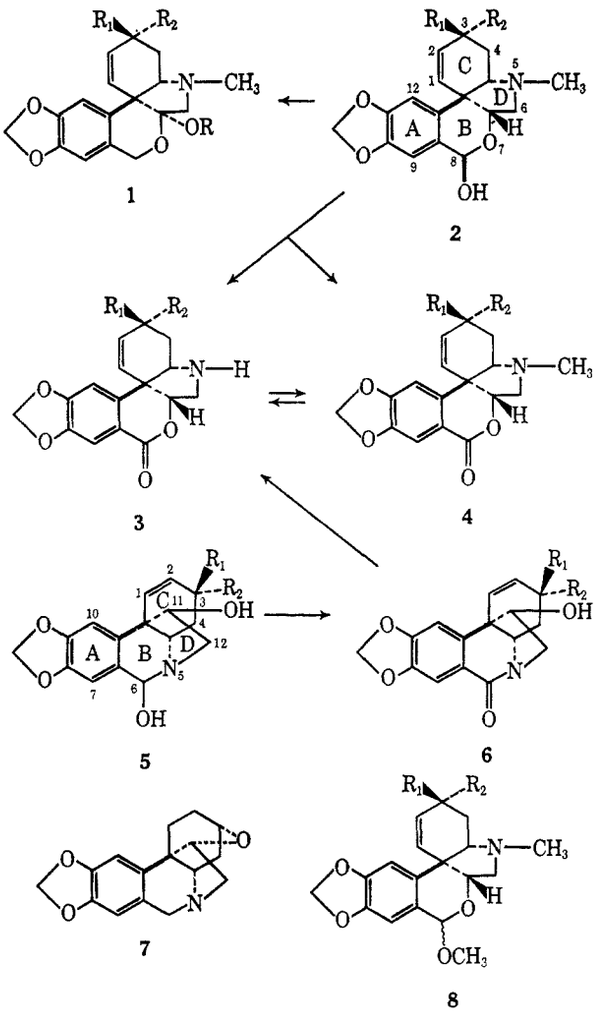
(15) W. C. Wildman and Carol J. Kaufman, *J. Amer. Chem. Soc.*, **76**, 5815 (1954).

(16) N. F. Proskurnina, *Zh. Obshch. Khim.*, **23**, 3365 (1957).

the two compounds is found in the nmr spectra. Tazettine contains a benzylic methylene AB pattern (4.78 ppm) which is not observed in the spectrum of pretazettine. The lack of this methylene pattern and the presence of a one-proton singlet (6.06 ppm) is evidence for a benzylic substitution of pretazettine. The presence of a benzylic hydroxyl group was confirmed by a manganese dioxide oxidation of pretazettine to a mixture of **3a** and **4a**. Both compounds have infrared and ultraviolet spectra consistent with a conjugated carbonyl function. The nmr spectrum of compound **4a** was similar to the starting material, except that the benzylic proton singlet at 6.06 ppm was absent and an aromatic proton, formerly found at 6.83 ppm, had been shifted to 7.51 ppm. These data indicate that the benzylic hydroxyl group had been oxidized to a carbonyl group with the concomitant loss of the benzylic proton. A carbonyl group at C_8 would explain the large shift in the adjacent aromatic proton. The nmr spectrum of **3a** was similar to that of **4a**, except for the absence of the N-methyl singlet (formerly at 2.52 ppm) and the presence of a single proton at 1.89 ppm, which was exchangeable with D_2O. This indicated that the N-methyl group had undergone oxidative cleavage.[17] The infrared spectrum of the crude oxidation mixture showed a weak band at 1671 cm^{-1} suggesting the presence of traces of the N-formyl intermediate (**4a**, N–CHO instead of N–CH_3). In subsequent experiments it was possible to convert **4a** into **3a** by manganese dioxide oxidation.

The structure and stereochemistry of **3a** and **4a** were proven by synthetic interconversions.[18] Haemanthidine (**5a**) was oxidized to 6-oxohaemanthamine (**6a**) by manganese dioxide.[19] Refluxing **6a** in a sodium acetate–acetic acid buffer gave a compound, the infrared and ultraviolet spectra of which showed the presence of a conjugated lactone rather than the original lactam. The ir and nmr spectra of the reaction product indicated that the tertiary amide group of **6a** had been converted into a secondary amine. This product can be explained by the hydrolysis of the lactam to an amino acid which has subsequently undergone lactonization between the carboxylic acid and the C_{11} hydroxyl group to provide **3a**. This product was identical in all respects with **3a** formed by the oxidation of pretazettine. N-Methylation of **3a** with formaldehyde and sodium borohydride gave **4a**.[20] By these conversions, the structure and stereochemistry of pretazettine (**2a**) and haemanthidine (**5a**) have been related.

The structure of haemanthidine (**5a**) has been proven by chemical conversions into apodihydrohaemanthamine[19] (**7**) and tazettine (**1a**, R = H).[21] These two compounds relate the structure of haemanthidine to haemanthamine (**5a**, no OH at C_6) and O-methylcriwelline[7c] (**1b**, R = CH_3). It has been shown by X-ray diffraction studies that 6-hydroxycrinamine has the



structure **5b**.[22] Since 6-hydroxycrinamine has been converted into O-methylcriwelline[9] (**1b**, R = CH_3), the basic structure assigned to haemanthidine (**5a**) seems secure.[23] Manganese dioxide oxidation of haemanthidine to the bridgehead lactam (**6a**) indicates the presence of a hydroxyl group at C_6. The characteristics of this amino alcohol have been discussed.[24] The location of a hydroxyl group at C_{11} can be assumed from the facile conversion into tazettine. The stereochemical configuration of this hydroxyl group is of primary importance for future postulates.

Hydrogen-bonding studies in the ir spectrum confirm that the configuration of the C_{11} hydroxyl group of haemanthidine is as shown in **5a**.[25] 6-Oxohaemanthamine shows a single hydroxyl stretching frequency at 3610 cm^{-1}. In contrast, 6-oxodihydrohaemanthamine has a hydroxyl stretching frequency at 3627 cm^{-1}. Thus, the C_{11} hydroxyl group of haemanthidine has a configuration in which this group is directed toward the C_1–C_2 unsaturation. This is consistent with the C_{11}

(17) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).

(18) Preliminary investigations carried out by Professor S. Uyeo at the National Heart Institute in 1958.

(19) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2590 (1958).

(20) Further isolations of minor alkaloids from *S. formosissima* gave a substance which was identical in all respects with **4a**. The new base was named 3-epimacronine because of the similarity of its structure with the alkaloid macronine[11] (**4b**).

(21) (a) H.-G. Boit and W. Stender, *Chem. Ber.*, **89**, 161 (1956); (b) W. C. Wildman, *Chem. Ind.* (London), 123 (1956).

(22) J. Karle, J. A. Estlin, and I. L. Karle, *J. Amer. Chem. Soc.*, **89**, 6510 (1967).

(23) The absolute configuration assigned for all structures in this paper rests on the report that tazettine has the absolute configuration shown in **1a**.[7a]

(24) R. W. King, C. F. Murphy, and W. C. Wildman, *ibid.*, **87**, 4912 (1965).

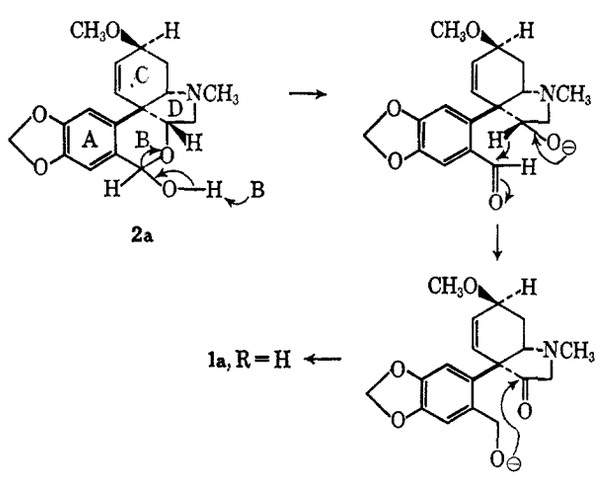
(25) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, unpublished data, 1958.

hydroxyl groups of haemanthamine, crinamine, and 6-hydroxycrinamine.

There is no reason to suspect that, under the mild reaction conditions, the configuration of the C_{11} hydroxyl group of 6-oxohaemanthamine has been altered in the transformation to **3a**. Therefore, the configuration of the C_{6a} hydrogen of **3a** and **4a** is β (steroid convention), and the B–D ring fusion is *trans*. This is in contrast to the *cis* B–D ring fusion found in tazettine. If the structures assigned to **3a** and **4a** are correct, pretazettine must also have a *trans* B–D ring fusion and a β C_6 hydrogen as shown in **2a**.[26]

The configuration of the C_8 benzylic hydroxyl group is the only feature of pretazettine left to be described. Recently, it has been shown that the alkaloids in the 5,10b-ethanophenanthridine nucleus having a benzylic hydroxyl group (**5**) exist in solution as a mixture of C_6 epimers.[24] Although the benzylic hydroxyl group of pretazettine gives no spectral indication of epimeric character, there is chemical evidence for this mobility. Pretazettine upon treatment with acidic methanol gave a mixture of C_8 epimeric acetals corresponding to α- and β-O-methylpretazettine (**8a**). The two acetals show slightly different R_f values by tlc, but all attempts to isolate the individual acetals were unsuccessful. Pretazettine was recovered after a mild acidic hydrolysis of the acetal mixture. The nmr spectrum of O-methylpretazettine is similar to that of pretazettine in showing only two aromatic protons and one benzylic proton. This indicates that the protons of the C_8 epimers of **2a** and **8a** must have equivalent chemical shifts.

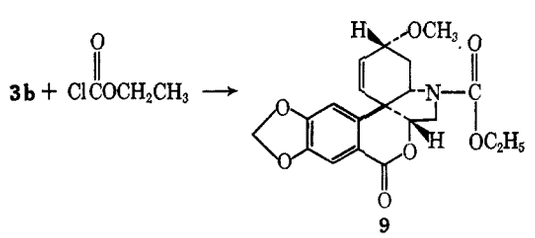
The mechanism for the rearrangement of pretazettine to tazettine appears to be similar to that proposed earlier for the conversion of haemanthidine and 6-hydroxycrinamine into tazettine and criwelline, respectively.[27] Pretazettine has a *trans* B–D ring fusion and is a relatively strained molecule. Tazettine has a *cis* B–D fusion which allows more flexibility. The driving force for the B-ring opening of **2a** would appear to be the relief of this internal strain. The completion of the rearrangement may be considered an intramolecular crossed-Cannizzaro reaction with subsequent hemiketal formation. This final closure occurs in such a way as to give the less strained *cis* B–D fusion of tazettine.



Isolations from *Crinum powellii* **Hort. var.** *album*.—The lability of pretazettine led us to doubt the natural occurrence of criwelline (**1b**). *Crinum powellii* was the original source of this alkaloid.[8] Other workers have reported isolating from this plant caranine, crinalbine, crinine, haemanthamine, ismine, lycorine, and powelline.[13,28] In a reinvestigation of this plant, bulbs were processed by the same isolation procedure used with *Sprekelia formosissima* to obtain pretazettine. Tlc of the total crude alkaloid fraction showed that criwelline was not present. Because the characteristic R_f values of precriwelline were not known, components of the mixture were separated by preparative tlc and identified by comparison of infrared spectra and physical properties with known alkaloids. One compound showed an infrared spectrum similar to that of pretazettine. It resisted crystallization but formed a crystalline hydrochloride salt, mp 199–201°. Treatment with dilute sodium hydroxide gave criwelline in good yield. Oxidation with manganese dioxide gave two compounds which were identified as macronine (**4b**) and N-demethylmacronine (**3b**) by tlc comparison. On the basis of these data and the similarity of this alkaloid with pretazettine, we consider this alkaloid to be precriwelline (**2b**).

Isolations from *Crinum erubescens* **Ait.**—Previous isolations from *Crinum erubescens* have shown the presence of crinamine, lycorine, 6-hydroxycrinamine, criwelline, and coranicine.[9,29] Use of the previously outlined mild isolation procedure and tlc techniques led to the isolation of a number of known alkaloids which had not been reported previously to occur in this plant. In addition, two new alkaloids containing the [2]benzopyrano[3,4-*c*]indole nucleus were found. Purification by tlc led to the isolation of a new alkaloid of moderate concentration in the plant. By all spectroscopic and chromatographic criteria it was identical with N-demethylmacronine (**3b**), known previously only by synthesis.[11]

The second alkaloid was present only in trace amounts. The uv and ir spectra showed many similarities with macronine (**4b**) and N-demethylmacronine (**3b**). However, the compound contained two carbonyl groups (1721, 1695 cm^{-1}). The nmr spectrum was also similar to those of **3b** and **4b** except for an additional two-proton quartet (4.16 ppm) and a three-proton triplet (1.28 ppm) which suggested an ethoxyl group. The mass spectrum indicated that the compound had a molecular weight of 387. These data would be consistent with the carbamate structure **9**.



To verify this hypothesis, N-demethylmacronine (**3b**) was treated with ethyl chloroformate. The product was identical in all respects with the natural alkaloid.

(26) The proof of structure of macronine involved a similar rearrangement utilizing 6-hydroxycrinamine (**5b**) as starting material.[11] The configuration of the C_{11} hydroxyl group of **5b** is known to be *anti* to the aromatic ring.[22] By similar reasoning macronine must also have a β C_{6a} hydrogen.

(27) C. F. Murphy and W. C. Wildman, *Tetrahedron Lett.*, 3863 (1964).

(28) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **47**, 498 (1960).

(29) C. F. Murphy, Ph.D. Thesis, Iowa State University, 1966.

An ethyl carbamate such as **9** is most suspect as a natural product and could well be an artifact derived from the chloroform and ethanol present in the plant processing procedure.

Experimental Section[30]

Alkaloid Isolation from *Sprekelia formosissima*.—Dormant bulbs (17.8 kg) were ground in 95% ethanol in a Waring Blendor. The plant material was extracted three times with 10 gal of 95% ethanol. The ethanolic solution was evaporated *in vacuo* to a volume of approximately 3 l., made acidic (pH 4) with tartaric acid, and extracted four times with benzene to remove the neutral material. The acidic solution was extracted four times with chloroform to provide 8.0 g of chloroform-soluble alkaloid hydrotartrates. The aqueous acidic solution was made basic (pH 8) with concentrated ammonium hydroxide and extracted four times with chloroform. The chloroform solution was evaporated *in vacuo* to give 46.0 g of crude alkaloids. Finally, the aqueous solution was raised to pH 10 with ammonium hydroxide and extracted three times with chloroform. This chloroform extract afforded 4.1 g of crude alkaloids. Tlc of each alkaloid fraction on silica gel plates developed in chloroform–methanol–diethylamine (92:3:5) failed to show the presence of any tazettine.

Alkaloid Isolation from *Ismene calithina*.—Growing bulbs (1.5 kg) were processed in the same manner as cited for *S. formosissima*. The following weights of chloroform extractable material were obtained: pH 4 fraction, 1.8 g; pH 8 fraction, 2.5 g; pH 10 fraction, 0.5 g. Tlc of the alkaloid fractions on silica gel plates developed in chloroform–methanol–diethylamine (92:3:5) failed to show the presence of any tazettine.

Pretazettine (2a).—Pretazettine was most easily isolated by column chromatography using silica gel packed in chloroform. Elution of the column with chloroform and 3% methanol in chloroform removed most of the other alkaloids of the crude fraction leaving pretazettine on the column. Chloroform–methanol (1:1) eluted the pretazettine (amorphous): $[\alpha]^{24}D$ +180 (*c* 0.2, $CHCl_3$); λ_{max} (95% EtOH) 238 mμ (ε 5060), 291 (4300); ir ($CHCl_3$), 1508, 1489, 1045, 942 (aromatic methylenedioxy), 3600 (–OH), 2832 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$), δ 6.75 and 6.83 (2 s, aromatic protons), 2.47 (s, $-NCH_3$), 3.42 (s, $-OCH_3$), 5.91 ppm (s, 2, methylenedioxy).

Pretazettine afforded a crystalline hydrochloride salt from ethanol: mp 224–225°; $[\alpha]^{24}D$ +30.3° (*c* 0.15, H_2O); λ_{max} (95% EtOH) 243 mμ (ε 3400), 290 (4000).

Anal. Calcd for $C_{18}H_{21}NO_5 \cdot HCl$: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.53; H, 6.18; N, 3.91.

Pretazettine hydrobromide crystallized from ethanol as colorless prisms: mp 224–226°; $[\alpha]^{24}D$ +19.4° (*c* 0.16, H_2O).

Anal. Calcd for $C_{18}H_{21}NO_5 \cdot HBr$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.29; H, 5.23; N, 3.43.

Conversion of Pretazettine (2a) into Tazettine (1a, R = H).

A.—A solution of 10 mg of pretazettine in 1 ml of 0.1 *N* sodium hydroxide was allowed to stand at room temperature. Tlc examination of the mixture after 30 min indicated that more than half of the pretazettine had rearranged to tazettine. In 1 hr the rearrangement was complete.

B.—A solution of 50 mg of pretazettine in 1 ml of chloroform was allowed to stand overnight at room temperature. Tlc examination of the mixture after standing 12 hr indicated that the rearrangement was approximately half completed.

C.—A solution of 10 mg of pretazettine in 1 ml of distilled water was heated at 70°. The rearrangement was complete in less than 1 hr.

D.—Pretazettine was stable in dilute aqueous acid. A solution of 20 mg of pretazettine in 2 ml of 0.2 *N* hydrochloric acid was refluxed for 12 hr. Examination of the solution indicated the presence of only pretazettine.

Tlc analysis in each case was carried out in chloroform–methanol–diethylamine (92:3:5): pretazettine, R_f 0.5; tazettine, R_f 0.7.

Manganese Dioxide Oxidation of Pretazettine.—A suspension of 3.067 g of manganese dioxide and 302 mg of pretazettine in 200 ml of chloroform (previously dried over K_2CO_3) was stirred at room temperature for 4 hr. The manganese dioxide was removed by filtration, and the filter cake was washed with chloroform. The chloroform solution was evaporated to dryness under reduced pressure to give 260 mg of residue which was separated by preparative tlc on silica gel using chloroform–methanol–diethylamine (92:3:5). The band at R_f 0.8 yielded 108 mg of 3-epimacronine (**4a**). The alkaloid afforded colorless prisms from acetone: mp 129–131°; $[\alpha]^{24}D$ +276° (*c* 0.95, $CHCl_3$); λ_{max} (95% EtOH) 227 mμ (ε 29,000), 267 (6100), 307 (6600); ir ($CHCl_3$), 1505, 1481, 1042, 940 (aromatic methylenedioxy), 1720 (C=O), 2832 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$), δ 6.75 and 7.51 (2 s, aromatic protons), 6.02 (s, 2, methylenedioxy), 3.41 (s, $-OCH_3$), 2.52 ppm (s, $-NCH_3$).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.55; H, 5.90; N, 4.20.

The band at R_f 0.6 provided 124 mg of N-demethyl-3-epimacronine (**3a**) which crystallized as prisms from ether–acetone: mp 154–155°; $[\alpha]^{24}D$ +207° (*c* 0.36, $CHCl_3$); λ_{max} (95% EtOH) 228 mμ (ε 31,400), 268 (6000), 308 (6800); ir ($CHCl_3$), 1508, 1484, 1042, 941 (aromatic methylenedioxy), 1721 (C=O), 2838 cm^{-1} ($-OCH_3$); nmr, ($CDCl_3$) δ 6.71 and 7.50 (2 s, aromatic protons), 6.02 (s, 2, methylenedioxy), 3.41 ppm (s, $-OCH_3$).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.76; H, 5.43; N, 4.44. Found: C, 64.78; H, 5.51; N, 4.53.

N-Demethyl-3-epimacronine (3a). A. From 3-Epimacronine (4a).—A suspension of 30 mg of 3-epimacronine (**4a**) and 300 mg of manganese dioxide in 25 ml of chloroform was stirred at room temperature for 4 hr. Tlc of the recovered residue showed that about half of the starting material had been converted into **3a** in this time.

B. From 6-Oxohaemanthamine (6a).—To a solution of 50 mg of 6-oxohaemanthamine dissolved in 3 ml of 95% ethanol was added a mixture of 0.45 ml of glacial acetic acid and 1.15 g of sodium acetate dissolved in 9 ml of water. The mixture was refluxed for 3 hr and then cooled. The solution was diluted to approximately 50 ml with water, made basic (pH 10) with ammonium hydroxide, and extracted four times with chloroform. The chloroform was dried with potassium carbonate and evaporated to dryness to provide 44 mg of a light yellow oil which crystallized on standing. The compound recrystallized from ether–acetone as prisms, mp 153–155°. The compound was identical with **3a** prepared from pretazettine.

3-Epimacronine (4a) from N-Demethyl-3-epimacronine (3a).—A solution of 50 mg of **3a** was dissolved in 5 ml of methanol containing 50 mg of boric acid and 0.5 ml of 37% formaldehyde. The solution was treated with 150 mg of sodium borohydride and allowed to stand for 30 min at room temperature. The reaction was stopped by the addition of 0.5 ml of acetic acid. The solution was diluted with water, made basic (pH 10) with ammonium hydroxide, and extracted three times with chloroform. The chloroform was dried with potassium carbonate and evaporated to dryness *in vacuo*. The residue was crystallized from acetone to give 36 mg of **4a**, mp 130–131°.

O-Methylpretazettine (8a).—A solution of 100 mg of pretazettine (**2a**) hydrochloride in 8 ml of methanol was acidified with 0.1 ml of concentrated hydrochloric acid and refluxed overnight. The solution was evaporated to dryness under reduced pressure. Water (10 ml), made basic to pH 10 with potassium carbonate, was added to the residue. The resulting aqueous mixture was extracted four times with chloroform. Evaporation of the chloroform gave 94 mg of residue which was chromatographed on a silica gel column packed in chloroform. Elution with chloroform afforded 32 mg of O-methylpretazettine. Further elution with 15% methanol in chloroform eluted 38 mg of pretazettine. The O-methylpretazettine defied all attempts at crystallization. The material probably consists of the two C_8 methoxyl epimers. Two substances were detected on silica gel tlc plates developed in chloroform–methanol–diethylamine (92:3:5): R_f 0.8 (amorphous); $[\alpha]^{24}D$ +180° (*c* 0.24, $CHCl_3$); λ_{max} (95% EtOH) 242 mμ (ε 5950), 589 (3600); nmr ($CDCl_3$), δ 6.76 (s, 2, aromatic

(30) Melting points were taken on a Kofler hot-stage apparatus and are corrected. Infrared spectra were obtained with a Beckman Model IR-12 spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrometer. Proton nmr spectra were obtained in deuteriochloroform using a Varian A-60 spectrometer. Mass spectra were recorded with an Atlas CH-4 mass spectrometer operating at 70 eV. Optical rotations were obtained with a JASCO Model 5 optical rotatory dispersion spectrometer. Tlc was carried out on 0.25- and 1.0-mm layers using silica gel $PF_{254+366}$ (Merck). Ultraviolet light of the appropriate wavelengths was used for identification. The proof of identity of two alkaloid samples was always carried out by comparison of melting points, mixture melting points, ir spectra, and chromatographic data.

protons), 5.88 (s, 2, methylenedioxy), 3.53 and 3.41 (2 s, $-OCH_3$), 2.48 ppm (s, $-NCH_3$).

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.22; H, 6.96; N, 4.07.

Hydrolysis of O-Methylpretazettine (8a).—A solution of 100 mg of O-methylpretazettine in 10 ml of dilute aqueous hydrochloric acid (pH 2) was allowed to stand at room temperature for 2 hr. The solution was made basic (pH 10) with potassium carbonate and extracted three times with chloroform. The extraction recovered 94 mg of pretazettine which was characterized and shown to be pure by ir spectroscopy and tlc.

Isolation of 3-Epimacronine (4a).—3-Epimacronine was isolated from the pH 8 alkaloid fraction of *S. formosissima*. The separation was carried out using preparative tlc in a series of solvent systems with the successive recovery of the band corresponding to synthetic 3-epimacronine. The effects of each purification could be observed by increase of carbonyl absorption in the infrared spectrum. The chromatography was carried out on silica gel in chloroform–methanol–diethylamine (92:3:5), ether–methanol–diethylamine (85:10:5), and ethyl acetate–methanol (4:1). The R_f values were, respectively, 0.6, 0.8, and 0.5 for 3-epimacronine in the solvent systems.

Precriwelline (2b).—Dormant bulbs (16.5 kg) of *C. powellii* were processed in the same manner as *S. formosissima*. Extraction with chloroform at pH 4 provided 25.3 g of basic material. Similar extractions at pH 8 and 10 provided 33.2 and 4.4 g, respectively, of alkaloidal mixtures. Lycorine (3.0 g) was removed from the pH 8 chloroform extraction by filtration. Precriwelline was separated from the other alkaloids of the pH 8 fraction by preparative thin layer silica gel chromatography by elution in methanol–ethyl acetate (50:50). The precriwelline essentially remained at the origin while all other alkaloids migrated to a significant extent. The band of lowest R_f was removed and eluted with a large volume of methanol. The free base is amorphous: $[\alpha]^{24}D$ +228° (*c* 0.18, $CHCl_3$); λ_{max} (95% EtOH) 242 mμ (ε 3010), 291 (3200); ir ($CHCl_3$), 1509, 1489, 1047, 942 (aromatic methylenedioxy), 2835 ($-OCH_3$), 3600 cm^{-1} (–OH); nmr ($CDCl_3$), δ 6.61 and 6.83 (2 s, two aromatic protons), 5.90 (s, 2, methylenedioxy), 248 (s, $-NCH_3$), 3.41 ppm (s, $-OCH_3$).

Precriwelline hydrochloride crystallized from water as needles: mp 199–201°; $[\alpha]^{24}D$ +82° (*c* 0.2, H_2O).

Anal. Calcd for $C_{18}H_{21}NO_5 \cdot HCl \cdot {}^1/_2H_2O$: C, 57.37; H, 6.15; N, 3.72. Found: C, 57.29; H, 6.36; N, 3.81.

Manganese Dioxide Oxidation of Precriwelline.—A solution of 20 mg of precriwelline in 30 ml of dry chloroform was stirred with 200 mg of manganese dioxide for 4 hr. The manganese dioxide was removed by filtration, and the chloroform was evaporated to yield 11 mg of an oil. Tlc indicated the presence of N-demethylmacronine (**3b**) and macronine (**4b**) in about equal amounts.

Alkaloid Isolation from *Crinum erubescens*.—Dormant bulbs (18.0 kg), processed as described for *S. formosissima*, provided 15.5 g of material by chloroform extraction at pH 2, 4.25 g from extraction at pH 8, and 7.8 g from extraction at pH 10. Lycorine (6.5 g) was removed from the pH 8 fraction by trituration with chloroform and filtration. Thin layer investigation of the pH 8 fraction allowed the isolation of the following known alkaloids: lycorine, crinine, coranicine, crinamine, macronine, 6-hydroxycrinamine, powelline, buphanidrine, flexinine, crinamidine, nerbowdine, and deacetylbowdensine.

Isolation of N-Demethylmacronine (3b).—The most nonpolar major compound of the pH 8 fraction from *C. erubescens* was recovered by preparative tlc using silica gel developed in chloroform–methanol–diethylamine (91:4:5). The desired band was removed, and the material was recovered from the silica gel by elution with methanol. The compound that crystallized from acetone, mp 176–177°, was identical with N-demethylmacronine prepared by synthesis.[11]

Isolation of N-Demethylcarboethoxymacronine (9).—From the nonpolar trace compounds of the pH 8 fraction from *C. erubescens*, a compound was isolated which had an R_f 0.8 on silica gel in chloroform–methanol–diethylamine (91:4:5). Although tlc in several solvent systems testified to the compound's purity, it remained amorphous: $[\alpha]^{24}D$ +313° (*c* 0.17, $CHCl_3$); λ_{max} (95% EtOH) 288 mμ (ε 29,300), 268 (5140), 308 (5840); ir ($CHCl_3$), 1508, 1482, 1041, 940 (aromatic methylenedioxy), 1721 (C=O lactone), 1695 (C=O carbamate), 2830 cm^{-1} ($-OCH_3$); nmr ($CDCl_3$), δ 6.66 and 7.52 (2 s, aromatic protons), 6.05 (s, 2, methylenedioxy), 3.34 (s, $-OCH_3$), 4.16 (q, 2, CH_3-CH_2OCO–), 1.28 ppm (t, 3, CH_3CH_2O–).

Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.24; H, 5.63; N, 3.61.

N-Demethylcarboethoxymacronine (9) from N-Demethylmacronine (3b).—A solution of 20 mg of N-demethylmacronine in 0.5 ml of chloroform was added to 4 ml of freshly distilled ethyl chloroformate. The solution was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure with the recovery of 22 mg of an oil. Tlc on silica gel developed in ethyl acetate–methanol (90:10) showed that the residue was pure. This material was identical with **9** by comparison of infrared spectral and chromatographic data.

Registry No.—**2a**, 17322-84-8; **2a** HCl, 17322-85-9; **2a** HBr, 17322-86-0; **2b**, 17245-16-8; **2b** HCl, 17245-17-9; **3a**, 17245-18-0; **4a**, 17322-73-5; **4b**, 2124-70-1; **5a**, 466-73-9; **8a**, 17245-21-5; **9**, 17245-22-6.