action of homopiperonylamine and formaldehyde, and mentioned an unanalyzed hydrobromide of m. p. 256–258°.

Acknowledgments.—We wish to express our appreciation to Dr. T. J. Webb and Mr. Walter A. Bastedo, Jr., for the ultraviolet absorption measurements, and to Dr. Klaus Unna of the Merck Institute for Therapeutic Research for the pharmacological test, and to Messrs. Douglass Hayman and Wilhelm Reiss for the microanalyses.

Summary

Erythraline, $C_{18}H_{19}NO_3$, contains one methoxy group and a methylenedioxy group. The nitrogen atom is tertiary, and in all probability is common to two nuclei of the molecule, since it was shown that the tetrahydro derivative was identical with dihydroerythramine. The unsaturation consists of two ethylenic double bonds and one benzenoid nucleus. Erythramine and erythraline appear to contain four nuclei exclusive of the methylenedioxy bridge.

The ultraviolet absorption spectra of these two alkaloids and dihydroerythramine were determined and the spectrum of the latter was found to be very similar to that of 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline.

Hydrastic acid was obtained from the oxidation of erythraline methohydroxide with potassium permanganate.

Nuclear formulations for erythramine and erythraline are suggested on the basis of the present facts.

RAHWAY, N. J. RECEIVED APRIL 3, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Erythrina Alkaloids. IX. Isolation and Characterization of Erysodine, Erysopine, Erysocine and Erysovine

BY KARL FOLKERS AND FRANK KONIUSZY

Previous studies[1,2] have shown that alkaloids of curare-like action are widely distributed among the species of the genus *Erythrina*. Although there was a wide variation in the potencies of the seeds of different species, there was considerable uniformity of the paralysis potency values of seeds of closely related species and this uniformity often extended to certain taxonomical divisions of the genus.

Reference[2] to *Erythrina glauca* Willd. shows that the sample Haigh 9170 had a paralysis potency value of 33,300, and this value was representative of several samples. Studies of the alkaloids of *Erythrina glauca* which were recently published[3] showed that this sample (Haigh 9170) contained 0.40% of a crude free alkaloidal fraction and from this the alkaloids erythraline, erythratine, and erythramine were isolated. Since erythramine and erythraline have an activity of 7 and 8 mg./kg. respectively for curare-like action in the frog,[3,4] it may be calculated that one gram of these seeds of *Erythrina glauca* would contain 4 mg. of the crude free alkaloidal fraction which should paralyze approximately 500 g. of frog, and yet the assay showed that one gram of these seeds would paralyze 33,300 g. of frog. It is obvious that much paralysis potency was not being removed, even though the removal of the chloroform soluble alkaloidal fraction exhausted the extract of what might be considered the classical alkaloidal fraction. This discrepancy between the potencies of extracts and alkaloids for *Erythrina glauca*, as well as for other species, developed during the chemical and pharmacological studies[1,2] carried on in collaboration with Dr. Klaus Unna of the Merck Institute for Therapeutic Research. The discrepancies were further revealed and explained by the following two experiments.

The aqueous test solution[1] on *Erythrina Berteroana* Urb. (Benitez 9159)[5] was active at a T. D. (threshold dose) of 0.5 ml./kg. frog. When this solution was made alkaline with sodium bicarbonate, exhaustively extracted with chloroform to remove the free alkaloidal fraction, neutralized, freed of chloroform, and retested on frogs, it still was active at 0.5 ml./kg. The free alkaloidal fraction was dissolved in water at the same con-

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[1] Folkers and Unna, *J. Am. Pharm. Assoc.*, **27**, 693 (1938).

[2] Folkers and Unna, *ibid.*, **28**, 1019 (1939).

[3] Folkers and Koniuszy, THIS JOURNAL, **62**, 436 (1940).

[4] Folkers and Koniuszy, *ibid.*, **61**, 3053 (1939).

[5] Cited in reference 1 as: *Erythrina neglecta*. The name was reduced to synonymy under *Erythrina Berteroana* in a recent taxonomical revision of the American species of *Erythrina*, Krukoff, *Britonnia*, **3**, No. 2, 205 (1939).

centration and found active at 2.0 ml./kg. Therefore, the original threshold dose was not a measure of the activity of the classical alkaloidal fraction, but rather that of a second fraction very soluble in water. Upon the original assumption that a glyco-alkaloidal fraction was present which was entirely insoluble in an organic solvent, the solution, exhausted of the ordinary alkaloidal fraction, was acidified with hydrochloric acid and refluxed. After cooling, treating with sodium bicarbonate, and extracting with chloroform, a new fraction of hydrolyzed or liberated alkaloidal bases was obtained. The aqueous solution, properly adjusted in *p*H, was now one-tenth as active in frogs, and the new fraction showed activity upon testing.

The above experiment when applied to an extract of seeds of *Erythrina glauca* (Haigh 9170) gave a solution of T. D. 0.04 ml./kg., which, after removal of the free alkaloidal fraction, showed a residual potency of T. D. 0.05 ml./kg. and, after an acid hydrolysis, showed a residual potency of 0.2 ml./kg. After a second acid hydrolysis, the residual potency was 2.0 ml./kg.

It is now apparent that these seeds contain besides the classical alkaloidal fraction[6] a second fraction in which the physiologically active nitrogen containing molecules are chemically bound in such a manner as to make them very water soluble and very insoluble in immiscible organic solvents.

In this paper are described experiments on extracts from seeds of several species of *Erythrina*, which were exhausted of the free alkaloidal fraction, hydrolyzed by adding hydrochloric acid and refluxing, and extracted to obtain the liberated alkaloidal fraction; followed by experiments on the isolation and characterization of four new alkaloids from these crude liberated alkaloidal fractions.

It is desirable now to explain the basis of the nomenclature for the new *Erythrina* alkaloids as they are being reported from this Laboratory. The stem "*erythr-*" has been selected for naming the alkaloids isolated from the free alkaloidal fraction of any species of *Erythrina;* thus, α- and β-erythroidine,[7] erythramine,[8] erythraline,[3] and erythratine[8] from different species. It seemed advisable for naming to select this stem from the generic name rather than to select names derived from the specific names, since most of these alkaloids occur in more than one species. For the same reason, the stem "*eryso-*" has been selected for naming the alkaloids isolated from the liberated alkaloidal fraction. The combined alkaloids are to be so named as to indicate the liberated alkaloid formed on hydrolysis.

The four new alkaloids herein described have been named erysodine, erysopine, erysocine, and erysovine and their sources are indicated in Table I by positive signs. It is evident from Table I that these four alkaloids are widely distributed in the genus. They exist closely associated, and since it was not always possible or feasible to examine critically every fraction from every species, it is very likely that further studies with larger amounts of seeds would result in the identification of other bases. However, it is felt that the major liberated alkaloids were identified in most cases.

TABLE I

ISOLATION OF ALKALOIDS

Plant	Alkaloids Erysodine	Erysopine	Erysocine	Erysovine
E. abyssinica Lam.	+	+		
E. sandwicensis Deg.	+	+	+	+
E. glauca Willd.	+	+		
E. Berteroana Urb.				+
E. americana Mill.	+		+	
E. Poeppigiana (Walp.) O. F. Cook	+		+	+
E. herbacea L.	+	+		
E. flabelliformis Kearny	+	+	+	+

Microanalyses have shown that erysopine has the empirical formula $C_{17}H_{19}NO_3$ and that it has one methoxyl group. Erysodine, erysocine, and erysovine are isomeric empirically and have the formula $C_{18}H_{21}NO_3$, and each has two methoxyl groups. Since all four of these alkaloids are liberated in a hydrolytic reaction, it is logical that each should possess a phenolic hydroxyl group as is evidenced by their solubility in dilute sodium hydroxide solution. Since erysopine has only one methoxyl group and is CH_2 lower in formula, it is obviously a desmethyl derivative, and its third oxygen atom must occur also as a phenolic hydroxyl group. The fact that erysopine gives a very characteristic green color with ferric chloride in acid solution suggests the presence of two ortho

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[6] This fraction has been designated as the *free* alkaloidal fraction to distinguish it from the alkaloidal fraction liberated by hydrolysis. The latter is designated as the *liberated* alkaloidal fraction, and the *combined* alkaloidal fraction designates this fraction before hydrolysis.

[7] Folkers and Major, THIS JOURNAL, **59**, 1580 (1937); Folkers and Koniuszy, Abstracts of Papers, 97th meeting of the American Chemical Society, Baltimore, Md., April, 1939, Division of Organic Chemistry, page 17.

[8] Folkers and Koniuszy, THIS JOURNAL, **61**, 1232 (1939).

phenolic hydroxyl groups[9] and is in agreement with the desmethyl formula and alkali solubility. A further fact indicating the presence of ortho hydroxyl groups is the unstability of erysopine in sodium hydroxide solution which, in a sense, is reminiscent of apomorphine. Neither of the four alkaloids showed the presence of an N-methyl group nor a C-methyl group. The presence of the methoxyl and phenolic hydroxyl groups presupposes the presence of at least one benzenoid nucleus in all four alkaloids.

One very characteristic feature of these four liberated alkaloids is their weakly basic character. They dissolve in aqueous hydrochloric acid, but at low concentrations of acid erysopine crystallized out as the free base. Erysodine dissolved in warm ethanol containing an excess of hydrogen chloride, but crystallized as the free base as the solvent cooled. This weak basicity distinguishes these liberated alkaloids from the free alkaloids isolated from the free alkaloidal fractions.

Erysopine possesses a low solubility in water, chloroform, and the alcohol solvents, and this property facilitates its isolation and purification. Erysodine, erysocine, and erysovine are extracted from water with chloroform and fractionated from ether, alcohol, or other solvents. It is pointed out that identification of the latter three alkaloids by melting point alone may be deceptive because mixtures frequently do not have depressed melting points. Here again, the specific rotations are as valuable a guide as they were for the free alkaloids. The isolation of these alkaloids with identical properties from more than one species and by varied procedures has aided in establishing their homogeneity.

These liberated alkaloids in their combined form in the extracts are hydrolyzed frequently at widely different rates. Erysodine in *E. abyssinica* and *E. sandwicensis* is so readily hydrolyzed that a certain portion of liberated erysodine is isolated with the free alkaloidal fraction, and the hydrolysis occurred during the clarification at 25° when the solution had been made acidic with hydrochloric acid. In some cases, erysopine was hydrolyzed only after a considerable period of refluxing. These differences were utilized to aid isolations and separations by making successive hydrolyses for various periods of time. Excessive acid or long continued hydrolysis initiated general decomposition and is to be avoided. Hydrolyses in sodium hydroxide solutions also liberated these bases, but this alkaline condition also caused a degradation of the hypaphorine into trimethylamine and indole and this latter unstable substance was thereby introduced into the liberated alkaloidal fraction. Because of this, and the unstability of erysopine in alkaline solution, and a greater general decomposition, the acid hydrolyses were preferred.

It is noteworthy that the yields of the liberated alkaloidal fractions often greatly exceed that of the free alkaloidal fractions; thus, there were 2.12% of crude liberated alkaloids and only 0.37%[8] of crude free alkaloids from *Erythrina sandwicensis.*

Hypaphorine was isolated anew from the seeds of *E. flabelliformis* (1.2%), *E. abyssinica* (0.6%), *E. herbacea* (0.5%), *E. Berteroana, E. americana,* and *E. poeppigiana.*

Erysodine, erysopine, erysocine, and erysovine are all highly active for curare-like action as tested pharmacologically on frogs, and such data will be published elsewhere when completed.

Studies on the constitution of these four erysoalkaloids, and the manner in which they are combined or exist prior to hydrolysis, will appear in future papers.

Experimental Part

General Remarks.—Certain *Erythrina* alkaloids in the combined form are so readily hydrolyzed at 25–35° in an aqueous solution containing hydrochloric acid that a certain amount of hydrolyzed alkaloid is formed. This liberated alkaloid then possesses the solubility properties of the normal free alkaloids and is isolated simultaneously with this latter fraction. After this fact was realized, the acidic (hydrochloric acid) aqueous extracts were clarified as quickly as possible, made alkaline immediately with sodium bicarbonate and extracted with chloroform to remove the free alkaloidal fraction. This procedure was called the "preferred" one.[1] The "alternative" one, which consisted of concentrating *in vacuo* the clarified acidic aqueous extracts for the crystallization of hypaphorine hydrochloride, refrigeration, filtration, etc., involved the presence of the acidic condition for a much longer period of time, and signified, therefore, a greater time for hydrolysis of the alkaloids in the combined form. Obviously, the "preferred" procedure will give a more accurate determination of the percentage of the free alkaloidal fraction present. This is particularly significant for those species which contain five to ten times more of the combined alkaloids than the free alkaloids, since a partial hydrolysis may liberate an amount of alkaloid equal to the free fraction. Although the aqueous solutions of the alcohol extractives are acidic from natural acids, it has been advisable to add the minimum amount of

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(9) 6,7-Dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline was found to give a deep green coloration with ferric chloride solution; Pyman, *J. Chem. Soc.*, **97**, 276 (1910).

hydrochloric acid to prevent emulsions during the clarification and to prevent loss of the free alkaloids by their dissolving in the clarifying solvents.

For most species of *Erythrina*, the "preferred" procedure allows very little, if any, hydrolysis of the combined alkaloids. A few will show some hydrolysis even when the acid condition is maintained for the utmost minimum clarification time; thus, the free alkaloidal fraction (680 mg., 0.8%) from 85 g. of seeds of *Erythrina abyssinica* Lam. (Forest Dept. 9179, Tanganyika, Africa), yielded 47.5 mg. or 0.06% of crude erysodine (which was crystallized to purity; m. p. 202–203°, $(\alpha)_D$ +249.3) when it was treated with 0.5 ml. of ethanol and refrigerated.

Isolation of Erysodine from the Free Alkaloidal Fraction Obtained by the Alternative Procedure from Erythrina sandwicensis Deg.—The ground seeds (3 kg.) of *Erythrina sandwicensis* Deg. (L. W. Bryan 9160), were extracted as described previously.[1] The ethanol extractives were dissolved in 2 liters of water containing 40 ml. of concentrated hydrochloric acid. The solution was clarified, concentrated *in vacuo*, refrigerated, and 28.2 g. (0.94%) of hypaphorine hydrochloride was filtered. The filtrate, made alkaline with sodium bicarbonate, was extracted with chloroform, etc. The free alkaloidal fraction weighed 13.6 g. (0.45%). It was treated with 15 ml. of absolute ethanol, 6.9 g. of sodium iodide, and 2.25 g. of glacial acetic acid. The mixture yielded 8.2 g. of crude erythramine hydriodide. The mother liquor was freed from alcohol and the residue was dissolved in water. The solution was made alkaline with sodium bicarbonate and extracted ten times with chloroform. The chloroform residue weighed 1.2141 g., and this was again converted to the iodides. No crystalline material formed, so the bases were recovered as before; yield, 871.1 mg. This residue was dissolved in 5 ml. of 12% hydrogen chloride in ethanol. White crystals (needles) separated; yield, 784.1 mg., 0.026%, m. p. 191°. This product was crude erysodine. It probably contained erysocine and/or erysovine. After five crystallizations from ethanol, crystals of the constant m. p. 204–205° were obtained; $(\alpha)^{27}_D$ +248, c = 0.311, ethanol. Since the crystals were halogen free, the base was too weak to form a hydrochloride. The alkaloid was named erysodine.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68; two $—OCH_3$ groups, 20.74. Found: C, 72.21, 71.98; H, 7.26, 7.17; N, 4.72, 4.83; $—OCH_3$, 19.99.

Another sample of erysodine showed on micro active hydrogen determination, 0.8, 1.0 (cold) and 1.10 (hot) active hydrogen atoms. A Kuhn–Roth $C—CH_3$ group determination was negative.

Isolation of Erysodine and Erysopine after Acid Hydrolysis of Final Solution from Erythrina sandwicensis Deg.—After the free alkaloidal fraction had been extracted with chloroform from the alkaline (sodium bicarbonate) solution (1255 ml.) derived from 3250 g. of seeds of *Erythrina sandwicensis* Deg. (L. W. Bryan 9160), the solution was neutralized with hydrochloric acid for storage. (In an acid solution, the combined alkaloids slowly hydrolyze. In an alkaline solution, hypaphorine slowly decomposes to yield indole.)

A 100-ml. portion of this solution was made alkaline with sodium bicarbonate and extracted fifteen times with chloroform. The first twelve extractions gave negligible quantities of residue, and the last three gave absolutely no residue; thus, the solution was proved free of residual free alkaloids. The solution was neutralized with concentrated hydrochloric acid and then treated with 1 ml. more. After refluxing the solution for five minutes, it was cooled, made alkaline with sodium bicarbonate, and extracted ten times with chloroform. The yield of extractives was 2.6754 g. or 1.04%; m. p. 193–196°. Three crystallizations of this crude alkaloid gave pure erysodine of m. p. 204–205° and $[\alpha]^{25}_D$ +248.8.

During the first recrystallization of the crude alkaloid of m. p. 193–196°, a few milligrams of a white base would not dissolve. This material was filtered; m. p. 233–234°. After recrystallization from a large volume of ethanol, it showed m. p. 240–241°, $[\alpha]^{25}_D$ +263.4, c = 0.291, 60% absolute ethanol and 40% glycerol by volume. It was pure erysopine, and identical with that isolated from *Erythrina glauca* Willd. It gave the green color when added to a ferric chloride solution containing a drop of hydrochloric acid.

In order to determine whether the five-minute hydrolysis period was sufficient for the extract from *Erythrina sandwicensis*, the alkaline solution was made acid as before and refluxed for fifteen minutes. After extraction, etc., only 38.1 mg. of bases was obtained; thus the hydrolysis was complete in solution with an acid ratio of 1 ml./100 ml. solution. When another 100-ml. portion of the neutralized solution, left from the free alkaloid extraction, was acidified at the ratio of 2.5 ml./100 ml. solution and refluxed for fifteen minutes, cooled, made alkaline with sodium bicarbonate, extracted with chloroform, etc., it yielded 3.7307 g. or 1.44% of hydrolyzed bases. The somewhat more acidic solution gave a better yield.

In another experiment, the methanol extractives from 200 g. of seeds amounted to 38.7 g. or 19.3%. They were dissolved in 20 ml. of water, and, by a careful preferred procedure, yielded 0.37% of the crude erythramine fraction,[8] and, by the use of 5 ml. of concentrated hydrochloric acid followed by refluxing for forty-five minutes, they yielded 4.2368 g. or 2.12% of hydrolyzed bases. This higher yield (2.12 over 1.44%) undoubtedly was due to the higher yield (19.3 over 12.6% of the alcohol extractives in the two cases; *i. e.*, the 200 g. quantity was extracted more thoroughly than the 3250 g. one. After recrystallization, the crude bases yielded 4.03 g. or 2% of pure erysodine of m. p. 202–203° and $[\alpha]_D$ +248.2. The melting point of erysodine varied somewhat with the rate of heating the bath.

Alkaline Hydrolysis of Final Solution from Erythrina sandwicensis Deg.—When 25 ml. of the final solution, derived from the 3250 g. quantity of seeds described above, was treated with enough solid sodium hydroxide to make a 20% solution, and allowed to stand at 20–25° for two hours, and extracted with chloroform ten times, it yielded 1.07 g. or 1.63% of hydrolyzed bases. Although the alkaline hydrolysis gave comparable yields of crude hydrolyzed bases, the acid hydrolysis was preferred since it caused much less extraneous decomposition.

Isolation of Erysocine and Erysovine by Fractional Crystallization of Erysodine Mother Liquors Derived from Erythrina sandwicensis Deg.—A quantity of 28.0 g. of crude hydrolyzed alkaloids derived from the 3250-g. quantity of seeds described above was taken for fractionation. After extraction with a hot mixture of 1200 ml. of anhydrous ether and 300 ml. of absolute ethanol, four grams of dark insoluble material was filtered off. The first crop from the filtrate yielded 12 g. of material of m. p. 201–203°, which on recrystallization gave 10.3 g. of pure erysodine of m. p. 204° and $[\alpha]_D$ +248.6, and these constants did not change with two more crystallizations. The second crop of m. p. 155° was treated with 1 liter of hot ether. The insoluble portion was filtered and the filtrate was concentrated to 100 ml. The crystals (1.06 g.) were filtered (m. p. 190°). The filtrate was concentrated to 10 ml. and 600 mg. of crystals of m. p. 155° was obtained. They were recrystallized from 400 ml. of ether. Large prisms (m. p. 172°, $[\alpha]_D$ +252.2) and small needles formed (m. p. 162°, $[\alpha]_D$ +239.1) and were readily separated. The former yielded pure erysovine on further recrystallization (m. p. 178°, $[\alpha]_D$ +252.2), and the latter yielded pure erysocine on further recrystallization (m. p. 162°, $[\alpha]_D$ +235.6).

Anal. Calcd. for $C_{18}H_{21}NO_3$ (erysocine): C, 72.21; H, 7.07; N, 4.68; —OCH_3, 20.74. Found: C, 72.17; H, 7.07; N, 4.75; —OCH_3, 19.11; N—CH_3, none; C—CH_3, none.

Isolation of Erysopine and Erysodine from Erythrina glauca Willd.—A quantity of 200 g. of seeds of *Erythrina glauca* Willd. (Haigh 9170) was extracted by the alternative procedure. The 100 ml. of neutralized solution left from the chloroform extraction of the free alkaloidal fraction was treated with 1 ml. of concentrated hydrochloric acid, refluxed for five minutes, cooled and made alkaline with sodium bicarbonate. The first chloroform extract was highly colored. During the second chloroform extraction, a white precipitate formed which was filtered. The filtrate was extracted an additional eight times. The solvent distillation left 677 mg. of bases (0.33%) which readily yielded pure erysodine of m. p. 202–203° and $[\alpha]_D$ +247.8 on recrystallization from ethanol.

The water and chloroform insoluble precipitate weighed 1.5 g. (0.75%); m. p. 240–242°; $[\alpha]_D$ +265.6, c = 0.191, 60 parts ethanol and 40 parts glycerol. After recrystallization from 300 ml. of absolute ethanol, it showed m. p. 241–242° and $[\alpha]_D$ +265.2. An alcohol solution treated with a drop of ferric chloride and hydrochloric acid gave a green color. This very characteristic alkaloid was named erysopine.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.91; one —OCH_3 group, 10.87. Found: C, 71.54; H, 6.93; N, 5.04. After crystallization again, it showed: C, 71.50; H, 6.90; N, 4.93; —OCH_3, 11.15; =N—CH_3, none.

Another acid hydrolysis of the extracted solution eventually yielded only 15.2 mg. (0.007%); evidently the hydrolysis under such conditions was complete.

Isolation of Erysovine from Erythrina Berteroana Urb.—A quantity of 200 g. of seeds of *Erythrina Berteroana* Urb. (9195) was extracted by the alternative procedure. The 128 ml. of solution, exhausted of the free alkaloidal fraction, was treated with 2.5 ml. of concentrated hydrochloric acid and refluxed for five minutes. The cooled solution, treated with sodium bicarbonate, yielded 76.7 mg. of bases by ten chloroform extractions. A second acid hydrolysis on the solution was made for two hours, and, after the eventual chloroform extractions, an additional 234.5 mg. of bases was obtained; thus, the total yield was only 0.15%. The combined bases were dissolved in 0.3 ml. of ethanol, and, after scratching the walls of the tube, crystals formed; yield 119.4 mg., m. p. 175–176.5°. Two recrystallizations gave crystals of constant m. p. 178–179.5°; yield 52.6 mg. (0.026%); $[\alpha]_D$ +252.0, c = 0.123, ethanol. This alkaloid was named erysovine.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68; two —OCH_3 groups, 20.74. Found: C, 72.35, 72.36; H, 7.03, 7.18; N, 4.71; —OCH_3, 20.11.

Isolation of Erysocine and Erysodine from Erythrina americana Mill.—The 400 ml. of neutralized solution, exhausted of the free alkaloidal fraction by the alternative procedure, from 630 g. of seeds of *Erythrina americana* Mill. (Palaez 9185) was treated with 8 ml. of concentrated hydrochloric acid and refluxed for five minutes. After making alkaline, extracting, etc., 694.2 mg. (0.11%) of bases was obtained. Six recrystallizations from ethanol yielded needles of m. p. 160–161°; $[\alpha]_D$ +238.1. This alkaloid was named erysocine. It did not give a color with a ferric chloride solution.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68; two —OCH_3 groups, 20.74. Found: C, 72.00; H, 6.92; —OCH_3, 18.98; =NCH_3, negative; C—CH_3, negative.

A second hydrolysis of solution by the same procedure for thirty minutes yielded 500.3 mg. (0.08%) of bases which yielded crude erysodine.

A third hydrolysis of forty-five minutes caused some decomposition, as evidenced by the formation of tar-like material. However, 420.9 mg. (0.07%) of bases was obtained, which on recrystallization yielded pure erysodine; m. p. 202–204°, $[\alpha]_D$ +249.3.

The fourth hydrolysis of one and one-half hours caused much tar formation, but, after chloroform distillation of the extracts, 296.7 mg. (0.05%) of yellow bases was obtained which yielded 33 mg. of crude erysodine.

The fifth hydrolysis of two hours yielded 479.8 mg. (0.08%) of a thin yellow oil which gave no crystalline product.

The total yield of hydrolyzed bases which gave crystalline products was only 0.31%, and the rate of hydrolytic liberation of erysodine from *Erythrina americana* was distinctly slower than that for *Erythrina sandwicensis*.

Isolation of Erysocine, Erysodine, and Erysovine from Erythrina poeppigiana (Walp.) O. F. Cook.—The 7300 ml. of neutralized solution, exhausted of the free alkaloidal fraction by the preferred procedure, from 8700 g. of seeds of *Erythrina poeppigiana* (Walp.) O. F. Cook (Wortley 9241) was treated with 146 ml. of concentrated hydrochloric acid and refluxed one and one-fourth hours. After making alkaline with sodium bicarbonate, extracting six hours continuously with chloroform, etc., the yield of hydrolyzed bases was 82 g. (0.94%). On treating this crude mixture with 40 ml. of ethanol, 46 g. of crystalline bases of m. p. 163–165° was obtained. The second crop was 1.56 g. of m. p. 199–201°. One crystallization of the first crop from ethanol yielded 40 g. of m. p. 160–162° and a second crystallization yielded 37.4 g. of m. p. 160–

TABLE II

DATA ON THE ISOLATION OF ALKALOIDS FROM SPECIES OF *Erythrina*

Plant	Collectors' names and specimen numbers	Amount seeds, g.	Acid hydrolysis[b] 1st T.	1st Y.	2nd T.	2nd Y.	3rd T.	3rd Y.	Total hydrolyzed alkaloids, %	Alkaloids
E. abyssinica Lam.	Forest Dept. 9179	100.0[a]	5	0.25	45	2.22	45	0.18	2.65	*c*
E. herbacea L.	*d*	158.2[g]	60	.1	60	1.07	60	.24	1.41	*e*
E. flabelliformis	Jones 9154	600.0[g]	5	.46	60	1.73	90	.31	2.50	*f*
Kearny	Jones 9154	295.0[g]	45	.05	60	1.63			1.68	*h*

[a] The free alkaloidal fraction removed by the alternative procedure. [b] By hydrochloric acid, T = time in minutes, y = % yield. [c] The first hydrolysis yelded 253.6 mg. of bases of which 25 mg. would not dissolve in 1.5 ml. of ethanol. The 25 mg. was recrystallized three times to yield pure erysopine; m. p. 241°, $[\alpha]_D$ +265. The second hydrolysis yielded similarly 199.8 mg. of erysopine and 1.02 g. of erysodine (recrystallized once); m. p. 202.5–204°, $[\alpha]_D$ +250.6. The third hydrolysis yielded also a mixture of erysodine and erysopine. [d] 124 g. of seeds of Brazol 9144 and 34.2 g. of seeds of Jordan 9155. [e] The first hydrolysis yielded very crude erysodine. The second yielded 282.5 mg. of water insoluble erysopine when the solution was made alkaline. Two recrystallizations yielded pure erysopine; m. p. 241°, $[\alpha]_D$ +265.0. The chloroform extraction yielded 1.41 g. of gum which gave pure erysodine after two recrystallizations; m. p. 200–202°, $[\alpha]_D$ +249.2. The third hydrolysis yielded crude erysopine. [f] The first hydrolysis gave a mixture of m. p. 175–180°. Two recrystallizations gave pure erysodine of m. p. 202–204° and $[\alpha]_D$ +249.1. The second crop of the first recrystallization was recrystallized to yield pure erysovine of m. p. 177–179°, and $[\alpha]_D$ +252. The second hydrolysis yielded 8.66 g. of mixed bases which yielded pure erysodine after two crystallizations; yield 4.48 g., m. p. 201.5–203.5°, $[\alpha]_D$ +248.7. The third hydrolysis yielded 664.4 mg. of water insoluble erysopine and 906 mg. of chloroform extracted bases. [g] The free alkaloidal fraction was removed by the preferred procedure. [h] The 4.8152 g. of bases was extracted with 400 ml. of ether and filtered. The filtrate yielded 481.1 mg. of crystals upon standing. Two recrystallizations of this material yielded 89 mg. of pure erysocine, m. p. 160–161°; $[\alpha]_D$ +234.1.

162°. Thus, the melting point did not change even though the product was still a mixture of bases. Therefore, 25 g. of this mixture was taken for fractional crystallization.

The 25 g. was treated with 1500 ml. of boiling anhydrous ether. The insoluble material (A) was filtered; the filtrate was concentrated to 200 ml., and after crystallization, 8.0 g. of pure erysocine of m. p. 160–162° and $[\alpha]_D$ +233.6 was obtained, and the mother liquor was found to contain essentially erysocine. The 16.3 g. of insoluble material (A) was treated with 500 ml. of boiling anhydrous ether and the insoluble material (B) was filtered; 11.8 g. The filtrate (C) yielded 3.63 g. of pure erysocine after concentration; m. p. 161–162°, $[\alpha]_D$ +234.6.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07. Found: C, 72.15; H, 7.05.

The mother liquor of the filtrate (C) on standing yielded a second crop of mixed needles and tiny granules. Some needles (D) were separated mechanically. The material (B) was treated with 800 ml. of anhydrous ether to yield 6.5 g. (E) of insoluble material, which was treated with 800 ml. of ether to yield 3.77 g. of insoluble material (F). Treatment of (F) with a final 800 ml. of ether left 1.23 g. of insoluble material (G) of m. p. 199–200°. Recrystallization of (G) from alcohol yielded pure erysodine of m. p. 201.5–202.5° and $[\alpha]_D$ +249.2. Concentration of the soluble fractions corresponding to (E, F, and G) yielded more erysodine, and from the mother liquor crops, mixtures of needles (D) and granules (erysodine) were obtained. Mechanical separation of the needles (D) and recrystallization yielded pure erysovine of m. p. 178°, and $[\alpha]_D$ +253.3.

From the 25 g. of starting material, the fractional crystallization yielded about 15 g. of erysocine, 7.5 g. of erysodine, and 0.5 g. of erysovine.

Alkaline Hydrolysis of Final Solution from Erythrina poeppigiana (Walp.) O. F. Cook.—A quantity of 256 ml. of solution, exhausted of the free alkaloidal fraction, equivalent to 200 g. of seeds of *Erythrina poeppigiana* (Walp.) O. F. Cook (Wortley 9241) was treated with sodium hydroxide to make a 1% solution and refluxed for fifteen minutes. The solution was neutralized with hydrochloric acid, then treated with sodium bicarbonate for liberation of the phenolic bases, and extracted with chloroform, etc. The yield of bases was only 100 mg. or 0.05%. The hypaphorine was undergoing decomposition during refluxing, as evidenced by the odor of trimethylamine.

Another 256 ml. portion of solution was treated with sodium hydroxide for a 4% solution and refluxed thirty minutes. The odor of trimethylamine from the decomposing hypaphorine was very pronounced. After treatment as above, the yield of bases was 649 mg. or 0.32%. An acid hydrolysis for a similar time would have yielded about three times as much hydrolyzed alkaloids.

Data of Other Species of Erythrina.—In the foregoing experimental part, the details of isolation of the four alkaloids with which this paper is concerned, have been described for several diverse situations. The data on *Erythrina herbacea* L., *Erythrina flabelliformis* Kearny, and additional data on *Erythrina abyssinica* Lam. are recorded in Table II, and were obtained by similar procedures as indicated in the Notes on Table II.

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Summary

Evidence is presented to show that the seeds of species of *Erythrina* contain another alkaloidal fraction besides what has been designated as the free (classical) alkaloidal fraction. This new fraction, designated the combined alkaloidal fraction, has been shown to yield on acid (preferably) or alkaline hydrolysis, a liberated alkaloidal fraction. From these liberated alkaloidal fractions of eight species of *Erythrina*, four new liberated *Erythrina* alkaloids were isolated and characterized.

A system of nomenclature for the *Erythrina* alkaloids has been adopted, and the four new ones herein described from the liberated fractions have been named erysodine ($C_{18}H_{21}NO_3$), erysopine ($C_{17}H_{19}NO_3$), erysocine ($C_{18}H_{21}NO_3$), and erysovine ($C_{18}H_{21}NO_3$).

These four new alkaloids are all active for curare-like action on frogs.

Certain preliminary facts on the functional groups and structures of these four alkaloids have been described, and additional data will be presented in future papers.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

A New Synthesis of Coronene

BY MELVIN S. NEWMAN[1]

Coronene, VII, has long aroused interest not only because of its symmetric graphite-like[2] structure but also because the problem of its synthesis has presented a challenge to the ingenuity of the organic chemist. When Scholl and Meyer[3] first announced its synthesis the senior author stated that he had been occupied at intervals over a period of twenty years in attempts to prepare this hydrocarbon. Others have also mentioned attempts in this direction[4] and the isolation of coronene from certain coal hydrogenation residues is claimed.[5]

Furthermore, there are certain problems relating to the structure of polycyclic aromatic hydrocarbons which can more satisfactorily be attacked with the aid of coronene than with any other related compound.[6] Specifically, Professor Pauling has indicated that the values of interatomic distances can be estimated by X-ray studies and that the diamagnetic anisotropy of coronene[7] may be determined by making magnetic measurements. In both cases the symmetry of coronene should be of great value in mathematical treatment of the results.[6]

With these facts in mind it was decided to attempt to develop a new synthesis for coronene. The method used is illustrated by the chart.

A new method for effecting pinacolic reduction made possible the over-all conversion of 7-methyl-1-tetralone, I, to the diene, II, in 75–85% yields. This remarkably high yield in accomplishing a type of transformation usually accompanied by low yields made desirable further experiments in order to test the generality of the method: the more so since poor yields of II were obtained by methods previously reported for similar conversions.[8,9] The results of these experiments will be communicated shortly.

The new method consisted in adding a small amount of mercuric chloride to a benzene–absolute alcohol solution of the ketone, I, containing freshly scratched aluminum foil. On heating a vigorous reaction ensued and after three hours of refluxing the aluminum was entirely dissolved. The pinacol fraction of the products thus formed was dehydrated by boiling with acetic acid and the diene, II, crystallized on cooling.

The addition of maleic anhydride to II proceeded smoothly in boiling xylene (compare Weid-

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[1] The Elizabeth Clay Howald Scholar for the year 1939–1940.

[2] By inspection of the formula it may be seen that there are two concentric hexagons of carbon atoms which are linked only to other carbons.

[3] Scholl and Meyer, *Ber.*, **65**, 902 (1932). Their synthesis is extremely difficult and indeed, it is a tribute to their skill that they succeeded at all.

[4] (a) von Braun, *ibid.*, **64**, 1787 (1931); (b) Clar and Wallenstein, *ibid.*, **64**, 2076 (1931); (c) Clar, *ibid.*, **65**, 857 (1932).

[5] French Patent 816,162, *Chem. Zentr.*, **108**, II, 3846 (1937).

[6] Communication from Professor Linus Pauling, California Institute of Technology, Pasadena, California.

[7] Pauling, *J. Chem. Phys.*, **4**, 673 (1936); see also Squire, *Compt. rend.*, **206**, 665 (1938).

[8] (a) Barnett and Lawrence, *J. Chem. Soc.*, 1104 (1935); (b) Gomberg and Bachmann, THIS JOURNAL, **49**, 241 (1927); (c) Elbs and Schmitz, *J. prakt. Chem.*, **51**, 591 (1895).

[9] Weidlich, *Ber.*, **71**, 1203 (1938).