Experimental[6]

(I) **1-Phenyl-3-N-diethylaminobutene-2-one-1.**—A mixture of benzoylacetone (5 g.), diethylamine (4.5 g., a one mol excess), and one small drop of concd. hydrochloric acid was heated (110°) in a sealed tube for thirty-six hours, and then allowed to stand at room temperature for ten days. The light orange solution was dissolved in ether and shaken with several portions of water to remove excess diethylamine. Most of the unreacted benzoylacetone was also removed in this process. Evaporation of the ether gave light yellow crystals (4.1 g.) which on recrystallization from low boiling petroleum ether gave almost colorless rods, m. p. 70–71°.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45; C, 77.36; H, 8.82. Found: N, 6.40; C, 77.48; H, 8.84.

This compound gave clear solutions with dilute mineral acids, which on heating reformed benzoylacetone.

(II) **α-N-Diethylaminobenzalacetophenone.**—To a cooled (0°) absolute ethyl alcohol (20 ml.) suspension of benzalacetophenone dibromide (20 g.), diethylamine (12.0 g., a two mol excess) was added rapidly with stirring. The dibromide dissolved and the solution turned a deep red color, evolving some heat. After standing at room temperature for eighteen hours the precipitated diethylamine hydrobromide (16.5 g.) was filtered from the mixture with the addition of dry ether to the solution. Evaporation of the solvent *in vacuo* gave a red oil, which crystallized on adding low boiling petroleum ether to give orange-red crystals (13.5 g.), m. p. 50–54°. Recrystallization from low boiling petroleum ether gave orange rosets, m. p. 51–53°.

Anal. Calcd. for $C_{19}H_{21}NO$: N, 5.01; C, 81.67; H, 7.58. Found: N, 5.00; C, 81.65; H, 7.60.

This product darkened on standing and developed an isocyanide-like odor. Its ether solution precipitated a colorless hydrochloride with dry hydrogen chloride, m. p. 106–110°, which dissolved in water to precipitate the orange unsaturated amino ketone.

Hydrolysis of (II).—Freshly recrystallized (II) (2.0 g.) was heated on the steam-bath (thirty minutes) with 15% sulfuric acid (25 cc.). The product was an oily solid (1.4 g.) which on recrystallizing from dilute alcohol gave colorless needles; m. p. 60–63°. This product gave better than a 90% yield of the phenylenediamine derivative of benzyl phenyl diketone, m. p. 98–99°.[7]

(III) **β-N-Diethylaminobenzalacetophenone.**—A mixture of dibenzoylmethane (5 g.), diethylamine (3.26 g., a one mol excess), and one small drop of concd. hydrochloric acid was heated (150°) in a sealed tube for sixty-six hours, and then allowed to stand at room temperature for sixteen days. The reaction mixture was worked up as for (I) to give a light yellow oil from which only dibenzoylmethane could be crystallized. However, on dissolving this oil in dry ether and passing in dry hydrogen chloride an oily hydrochloride was precipitated. This product was well washed with ether and then decomposed in a saturated solution of sodium bicarbonate. This decomposition was carried out in a separatory funnel in the presence of ether, and the precipitated amino-ketone was immediately extracted from the aqueous layer. Evaporation of the ether gave an almost colorless solid (0.65 g.), m. p. 58–59°, which on recrystallization from low boiling petroleum ether gave almost colorless rods, m. p. 61–62°. The product had all of the properties of the product of André,[1] being completely soluble in mineral acids, from which it is precipitated unchanged by dilute alkali.

(6) All analyses for nitrogen were determined by the Kjeldahl method by Mr. Clifford Hollenbeck of the Graduate College of the University of Nebraska, and micro C–H analyses by Mr. Edward Renfrew of the University of Minnesota.

(7) Jörlander, *Ber.*, **50**, 416 (1917).

Summary

One new α-dialkylamino-α,β-unsaturated ketone, and a new β-dialkylamino-α,β-unsaturated ketone have been prepared from readily available starting materials, in good yields.

LINCOLN, NEBRASKA RECEIVED APRIL 8, 1940

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

Erythrina Alkaloids. VIII. Studies on the Constitution of Erythramine and Erythraline

BY KARL FOLKERS AND FRANK KONIUSZY

Erythramine was isolated originally from the seeds of *Erythrina sandwicensis* Deg. and *Erythrina subumbrans* (Hassk.) Merr.[1] It was later isolated from the seeds of *Erythrina glauca* Willd. together with erythraline and erythratine,[2] and the alkaloid erythraline was isolated from five additional species of *Erythrina*. Although the isolation of erythramine from *Erythrina glauca* was facilitated by large amounts of seeds, it is probable that many species which have yielded and will yield erythraline also contain erythramine. Since these species yielding erythramine and erythraline represent several groups and subgroups of the genus,[3] it seems probable that knowledge on the constitution of these two alkaloids will be significant for at least one broad group of *Erythrina* alkaloids.

(1) Folkers and Koniuszy, THIS JOURNAL, **61**, 1232 (1939).

(2) Folkers and Koniuszy, *ibid.*, **62**, 436 (1940).

(3) Krukoff, *Brittonia*, **3**, No. 2, 205 (1939); Krukoff, *J. Arnold Arboretum*, **20**, 225 (1939); Folkers and Unna, *J. Am. Pharm. Assoc.*, **28**, 1019 (1939).

The initial studies on the constitution of erythramine, $C_{18}H_{21}NO_3$, showed[4] that it possesses a methylenedioxy group, a methoxy group, a tertiary nitrogen atom which is probably common to two nuclei, and an ethylenic double bond. It consists apparently of four fused nuclei (exclusive of the methylenedioxy bridge), three being hydroaromatic and one aromatic.

Examination of erythraline, $C_{18}H_{19}NO_3$, has now shown that it also possesses a methylenedioxy group, one methoxy group, no N-methyl group, and a tertiary nitrogen atom since it formed a methiodide. This evidence, combined with the fact that empirically it has two hydrogen atoms less than erythramine, suggested that one more ethylenic bond was the only point of structural difference between erythraline and erythramine; consequently, erythraline was subjected to hydrogenation over a platinum catalyst. It absorbed two moles of hydrogen and the tetrahydroerythraline was found to be identical with dihydroerythramine[3] when the free bases and the hydriodides were compared.

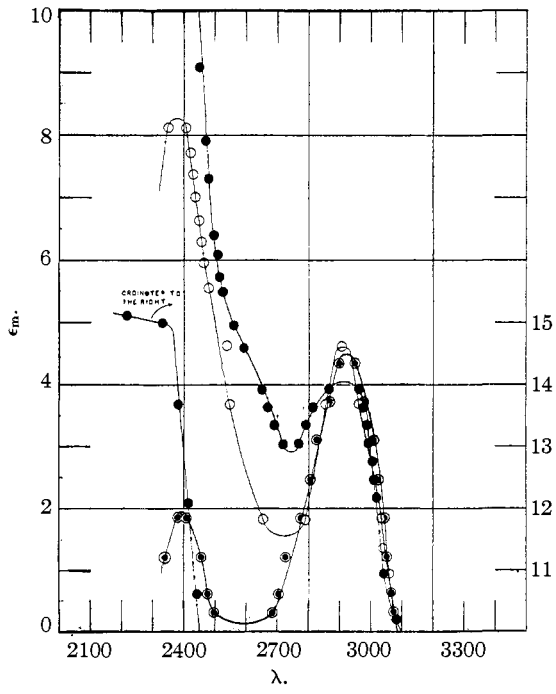


Fig. 1.—Absorption spectra in ethanol for: ●, erythraline base (note for erythraline that the ordinates are indicated *on the right* for ϵ_m, 10–15); ○, erythramine base; ◉, dihydroerythramine base. Absorptions are represented in terms of the extinction coefficient computed on the basis of one millimole per liter; wave lengths, in Ångström units.

(4) Folkers and Koniuszy, THIS JOURNAL, **61**, 3053 (1939).

The ultraviolet absorption spectra of erythramine and erythraline bases are shown in Fig. 1. It is seen that both alkaloids exhibit a band at approximately 2910 Å. and of similar intensities. Since it is probable that the absorption is influenced by the ethylenic unsaturation of these bases, the spectrum of dihydroerythramine (tetrahydroerythraline) base was determined and the curve is shown also in Fig. 1. It seemed appropriate to compare the spectrum of the dihydroerythramine with the spectra of known substances. For this purpose, the ultraviolet absorption spectra of hydrocotarnine[5] and 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrobromide[6] were determined and the curves are shown in Fig. 2 with that of dihydroerythramine hydrobromide. The very close similarity of the absorption of dihydroerythramine to that of the methylenedioxytetrahydroisoquinoline derivative and the dissimilarity to that of hydrocotarnine strongly indicated that the alkaloids have the partial nucleus I and not II. If this partial nucleus I were correct, then oxidation of such alkaloidal tetra-

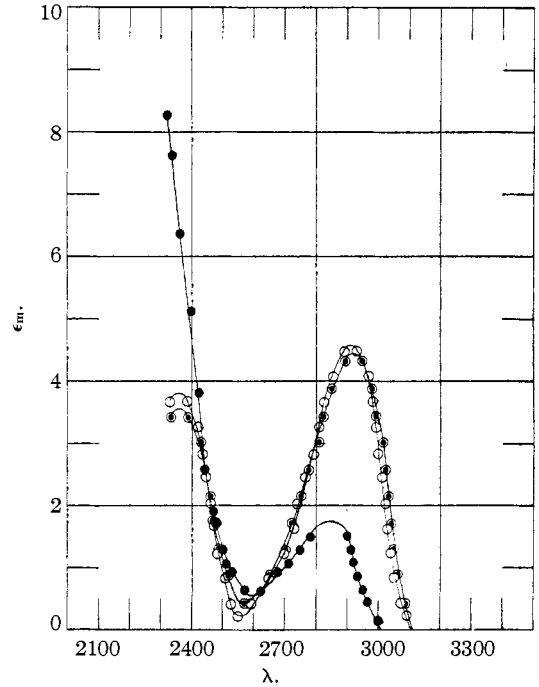
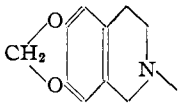


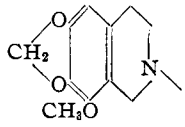
Fig. 2.—Absorption spectra in ethanol for: ●, hydrocotarnine; ○, dihydroerythramine hydrobromide; ◉, 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrobromide.

(5) Steiner, *Compt. rend.*, **176**, 1379 (1923); **176**, 244 (1923).

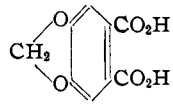
(6) For data on the N-methyl derivative, which is hydrohydrastinine, see Dobbie and Tinkler, *J. Chem. Soc.*, **85**, 1005 (1904).



I



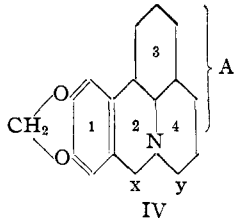
II



III

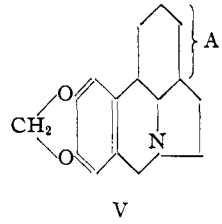
hydroisoquinoline derivatives should yield hydrastic acid, III. Erythraline methohydroxide was oxidized with potassium permanganate and an *o*-dicarboxylic acid was isolated as its methylimide derivative which proved to be $C_{10}H_7NO_4$. This substance was found to be identical with a synthetic specimen of hydrastic acid methylimide. Thus, the partial nucleus I is proved correct for erythramine and erythraline.

These various facts, and in particular the formation of hydrastic acid by oxidation, the ultraviolet absorption spectra, the tertiary nitrogen atom common to two of the four (exclusive of the methylenedioxy bridge) nuclei, allow certain nuclear formulations to be made for erythramine and erythraline. Of the possible nuclear structures for four six-atom nuclei, the one represented by IV appears to be the most probable. The positions of the rings 1 and 2 seem quite definite on the basis of the oxidation reaction and the absorption spectra. Ring 4 would be placed thus because of the tertiary nitrogen atom, and



IV

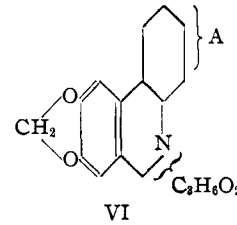
A = CH_3O— and one double bond for erythramine
A = CH_3O— and two double bonds for erythraline



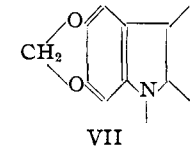
V

A = two HO— groups and one double bond

ring 3 would be so placed because this formulation is that of a hydrophenanthridine derivative. The alternative position of ring 3 at carbon atoms x and y would give a structure with a nitrogen atom centrally located in three nuclei, and such a grouping seems improbable to us for a natural alkaloid. The formulation, IV, would bear close relationship with the structure assigned[7] to lycorine, V, of the *Lycoris* alkaloids. However, the presence of one five-atom nucleus is not excluded, and this possibility suggests a relationship to the structure, VI, assigned to tazettine,[8] also of the *Lycoris* alkaloids. One inescapable fact on structural detail which is now apparent is that the methoxy group of erythramine and erythraline is attached to a hydroaromatic nucleus, and this rather uncommon structural detail is also noted for tazettine as formulated in VI. The structure of these two *Erythrina* alkaloids is being studied further.



VI



VII

A = CH_3O— and one double bond.

It is noteworthy that the formation of hydrastic acid excludes the hydroindole formulation, VII, which might be anticipated because of the accompanying hypaphorine in these seeds of species of *Erythrina*.

A possible relationship between the *Erythrina* alkaloids of the *Papilionaceae* with the *Lycoris* alkaloids of the *Amaryllidaceae* has no botanical justification. However, it is not unusual to find similarity and even identity in alkaloidal structure between the alkaloids elaborated by different families of plants.

Erythraline methiodide showed curare-like action in frogs at a threshold dose of 50 mg./kg., but was one-seventh as active as erythraline.[2] This same relationship between the activities of the quaternary and tertiary bases was noted for erythramine.[4]

Experimental Part

The Oxygen Atoms of Erythraline.—A Friedrich determination showed 10.56% —OCH_3 group and no =NCH_3 group; theory, one —OCH_3, 10.43%.

A 20-mg. sample of erythraline was dissolved in 5 ml. of 40% sulfuric acid and 60 mg. of phloroglucinol was added. Similar mixtures were made with erythramine and hydrocotarnine. The fourth tube contained only the reagents without an alkaloid. The tubes were heated in boiling water for twenty minutes. A red precipitate formed in the tubes containing the erythraline, erythramine, and hydrocotarnine; thus, erythraline possesses a methylenedioxy group.[9]

Erythraline Methiodide.—A quantity of 2.02 g. of pure erythraline hydriodide was converted to the free base by dissolving in water, adding sodium bicarbonate, extracting with chloroform, etc. The 1.8 g. of clear gum base was dissolved in 10 ml. of a 50–50 mixture of absolute methanol and benzene, and treated with 3 ml. of methyl iodide. After fifteen hours at 10°, the slightly yellow crystals were filtered. They softened at 96–98° and melted at 185–187°.

(7) Kondo and Uyeo, *Ber.*, **70**, 1087 (1937).
(8) Späth and Kahovec, *ibid.*, **67**, 1501 (1934).
(9) Gadamer and Winterfeld, *Arch. pharm.*, **262**, 601 (1924).

A sample was dried at 78° and 2 mm. for one hour before analysis.

Anal. Calcd. for $C_{18}H_{19}NO_3 \cdot CH_3I$: C, 51.90; H, 5.04. Found: C, 52.00; H, 5.07.

Hydrogenation of Erythraline to Tetrahydroerythraline and its Identity with Dihydroerythramine.—A 157 mg. quantity of pure erythraline base was dissolved in 50 ml. of water containing one drop of concentrated hydrochloric acid. The hydrogenation was made with 103 mg. of Adams platinum catalyst and under two atmospheres pressure. Two moles of hydrogen were absorbed. After catalyst filtration, the solution was made alkaline with sodium bicarbonate and extracted with chloroform, etc. The yield of colorless gum was 144 mg. This gum was dissolved in 25 ml. of anhydrous ether and 15 ml. of petroleum ether was added. Flocculent material was filtered, and the solution was concentrated to about 5 ml. On cooling and scratching, crystallization started. After one recrystallization, the crystals showed m. p. 81–84°, but were not pure. Therefore, they were converted to the hydriodide for purification. The purified hydriodide showed m. p. 215–216°. A sample was dried at 140° and 2 mm. for two hours before analysis.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot HI$: C, 50.35; H, 5.63. Found: C, 50.22; H, 5.57.

The tetrahydroerythraline hydriodide of m. p. 215–216° showed the m. p. 215–217° when mixed with dihydroerythramine hydriodide of m. p. 216–217°. Since certain *Erythrina* alkaloidal hydriodides showed little or no depression of mixed melting points, the purified hydriodide was reconverted to the free base. The white crystalline tetrahydroerythraline base (from ethyl ether and petroleum ether) showed m. p. 89–90°. This melting point was not depressed when the crystals were mixed with dihydroerythramine.

Oxidation of Erythraline Methohydroxide.—The 495 mg. of erythraline base obtained from 656 mg. of pure erythraline hydriodide was dissolved in 5 ml. of absolute methanol and treated with 1 ml. of methyl iodide. After warming for five minutes on the steam-bath, the solvents were removed *in vacuo* and the residual methiodide was dissolved in 60 ml. of water. This solution was stirred at 25° and treated dropwise with 200 ml. of 2.5% potassium permanganate solution. The pink color was now lasting. The solution was acidified with 10 ml. of concentrated hydrochloric acid and sulfur dioxide was passed through the solution until all the manganese dioxide had reacted. The clear solution was then extracted continuously with 400 ml. of ether for three hours. The 210 mg. of residue obtained by ether distillation was dissolved in 25 ml. of 5% ammonium hydroxide and the insoluble portion was filtered. Saturated calcium chloride solution was added to the filtrate until no further precipitation occurred. The calcium oxalate was filtered and the filtrate was acidified with hydrochloric acid. The solution was extracted continuously for two hours with ether. A residue of 39 mg. was obtained and sublimed at 150–170° at 2.5×10^{-4} mm. The sublimate, weighing 20.4 mg., was dissolved in water, treated with an excess of methylamine solution, and the solution concentrated to dryness. The residue was heated at 180–190° and 20 mm. in a sublimation apparatus. The solid on the cold finger was recrystallized from ethanol, m. p. 228°.

Anal. Calcd. for $C_{10}H_7NO_4$: C, 58.58; H, 3.44. Found: C, 58.31; H, 3.67.

This substance is proved to be the methylimide of hydrastic acid by its analysis, melting point, and mixed melting point (no depression) with a sample of the synthetic imide which melted at 228–228.5°.[8]

Synthesis of Hydrastic Acid.—The hydrastic acid was synthesized through the compounds piperonal, piperonylic acid, methyl piperonylate, methyl 6-nitro-piperonylate, methyl 6-amino-piperonylate, methyl 6-cyano-piperonylate, and hydrastic acid as described by Oertly and Pictet.[10] The nitro compound was hydrogenated with Adams platinum catalyst. The directions of Oertly and Pictet were very meager for the preparation of the cyano derivative and several attempts at repetition resulted in failure; therefore, the following procedure was devised.

Methyl 6-Cyano-piperonylate.—A 0.5-g. quantity of methyl 6-amino-piperonylate dissolved in 15 ml. of glacial acid acid was cooled to 0° and mixed with 25 ml. of concentrated sulfuric acid (also at 0°) containing 1 g. of sodium nitrate.

To a boiling solution of 8 g. of copper sulfate in 150 ml. of water was added 15 g. of sodium cyanide. After this boiling solution became homogeneous, the cold sulfuric acid solution was added dropwise (efficient hood). The mixture was allowed to cool to 25°. The buff-colored precipitate was filtered and washed twice with acetone. The washings were returned to the filtrate and the whole was extracted ten times with benzene. The benzene extract was washed twice with 5% sodium carbonate and concentrated to dryness. The yield of methyl 6-cyano-piperonylate was 168 mg. (30%); m. p. 134–135°. When recrystallized once from ether, it showed m. p. 135–136°.

6,7-Methylenedioxy-3,4-dihydroisoquinoline.—A mixture of 3.122 g. of pure homopiperonylamine and 0.881 g. of formic acid was refluxed for four hours. The product was dissolved in 50 ml. of anhydrous toluene and, while the solution was gently boiled, a 20-g. quantity of phosphorus pentoxide (weighed out in toluene) was added over twenty minutes. The refluxing mixture was well stirred. After cooling, 50 ml. of water was added. The toluene layer was discarded, and the residual toluene was removed by ether extraction. The aqueous solution was made alkaline with 15% sodium hydroxide solution and extracted continuously for two hours with ether. The ethereal solution was dried over potassium carbonate and distilled; yield, 0.836 g. (25.5%). The colorless oil solidified.

6,7 - Methylenedioxy - 1,2,3,4 - tetrahydroisoquinoline Hydrobromide.—A 575-mg. quantity of the dihydroisoquinoline derivative was dissolved in 100 ml. of dry benzene and hydrogenated at atmospheric pressure over 50 mg. of Adams platinum catalyst. Absorption ceased (one mole) after one hour. Dry hydrogen bromide was passed into the catalyst free filtrate. The white precipitate was filtered and recrystallized seven times from absolute methanol. The m. p. 255–256° was constant after the first recrystallization.

Anal. Calcd. for $C_{10}H_{11}NO_2 \cdot HBr$: C, 46.51; H, 4.64. Found: C, 46.57; H, 4.68.

Decker and Becker[11] prepared this compound by the re-

(10) Oertly and Pictet, *Ber.*, **43**, 1337 (1910).

(11) Decker and Becker, *Ann.*, **395**, 342 (1913).

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-

(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).