but none when mixed with the phthalide, III, obtained both from Friedel–Crafts and Grignard condensations.

Anal.[16] Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.4. Found: C, 83.7; H, 5.0.

Separation of Acid Mixtures into Components.—In a typical separation 9.42 g. of acid mixture, m. p. 115–150° (Friedel–Crafts), was dissolved in 100 cc. of absolute methanol saturated with hydrogen chloride. After refluxing for four hours the alcohol was partly distilled and the cooled solution poured into 150 cc. of water. The product was carefully taken into ether and the unreacted acid recovered by extraction with alkali. The ethereal solution was dried and the ester mixture vacuum distilled. The nearly colorless distillate, 9.3 g., b. p. about 184–187° at 6 mm., was stirred into 50 cc. of concentrated sulfuric acid giving an orange solution. After five minutes this solution was poured into 250 cc. of water whereupon all color vanished. The organic matter was carefully separated into acid and neutral fractions as usual. Crystallization of the acid fraction from benzene yielded 2.90 g. of 2-benzoyl-6-methylbenzoic acid, I, m. p. 123–125°. The neutral fraction was crystallized from a small amount of methanol and yielded 5.04 g. of the normal methyl ester of 2-benzoyl-3-methylbenzoic acid, II, which melted at 102–105°. Upon alkaline hydrolysis this was converted in 94% yield into II, m. p. 172.0–172.9°. The remaining acid had a slightly lower melting point and a wider melting range. The other separations of acid fractions were carried out in the same way and the averaged results are indicated in the Chart. The 36.6% figure in parentheses above formula I in the Chart is the result of taking into account the quantity of III obtained in the Friedel–Crafts reactions. The 44.0% figure below is similarly corrected. As a result of several runs we estimate that the various values may be reproduced to within 5%.

(16) Analysis by Mr. D. Mowry.

Summary

It is shown that on condensation of 3-methylphthalic anhydride with phenylmagnesium bromide the reaction takes place preferentially at the unhindered carbonyl group, the ratio of 2-benzoyl-6-methylbenzoic acid, I, to 2-benzoyl-3-methylbenzoic acid, II, formed being about 3.5. In the Friedel–Crafts condensation reaction at the two carbonyl groups takes place in approximately equal amounts.

An efficient method for separating mixtures of I and II is described. This method is based on a preferential hydrolysis of the methyl esters of I and II by concentrated sulfuric acid.

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

Erythrina Alkaloids. X. Isolation and Characterization of Erysonine and Other Liberated Alkaloids

BY KARL FOLKERS, JOHN SHAVEL, JR., AND FRANK KONIUSZY

β-Erythroidine hydrochloride was given first to dogs[1] and then to humans[2] for the modification of the severity of the metrazol convulsion, thereby preventing fractures of bones, in the convulsive therapy of the psychoses. The results of Rosen and his co-workers have encouraged our continued study of the alkaloids of hitherto chemically unexamined species of *Erythrina*.

It was shown previously[3] that seeds of species of *Erythrina* contain another alkaloidal fraction in addition to the free alkaloidal fraction or the classical combination of the nitrogen bases and organic acids. This new fraction was designated the combined alkaloidal fraction because the nitrogen bases were found to be united with other molecules. This was shown by the fact that the combined molecules in aqueous solution were unextractable by the immiscible solvents, and that on acid (preferably) or alkaline hydrolysis, they yielded a solvent soluble fraction, which was designated the liberated alkaloidal fraction. From the liberated bases of eight species of *Erythrina*, four new *Erythrina* alkaloids were isolated: erysodine, erysopine, erysocine and erysovine.[4]

This paper summarizes the pertinent and interesting data resulting from the examination of the liberated alkaloidal fractions obtained from nine additional species of *Erythrina*.[5]

Erysodine and erysopine were isolated again from many of these nine species. One new alkaloid has been isolated from certain samples of *Erythrina costaricensis* Micheli and it has been

(1) Rosen, Ziegler and Cominole, *J. Am. Pharm. Assoc.*, **29**, 164 (1940).

(2) Rosen, Cameron and Ziegler, *Psychiatric Quart.*, **14**, 477 (1940).

(3) Folkers and Koniuszy, THIS JOURNAL, **62**, 1677 (1940).

(4) The stem "eryso-" was selected for naming the liberated alkaloids, and the stem "erythr-" was used for naming the free alkaloids.

(5) The identity of the *Erythrina* seeds was established by Mr. B. A. Krukoff at the New York Botanical Garden either by determination of accompanying herbarium material or by other evidence which left no doubt regarding the identity.

named erysonine. The sources of these three eryso- alkaloids are indicated by positive signs in Table I.

TABLE I

ISOLATION OF ALKALOIDS

Plant	Alkaloids: Erysodine	Erysopine	Erysonine
E. crista-galli L.	+	+	
E. costaricensis Micheli	+	+	+
E. subumbrans (Hassk.) Merr.	+	+	
E. Dominguezii Hassler	+	+	
E. macrophylla DC.	+	+	
E. acanthocarpa E. Mey		+	
E. rubrinervia H.B.K.		+	
E. senegalensis DC.	+	+	
E. fusca Lour.	+	+	

The widespread occurrence of erysodine and erysopine throughout the genus *Erythrina* is readily realized when it is noted that the species listed in Tables I in this paper and paper IX represent many sections and groups of the genus as they were tabulated previously.[6] In these studies, an examination of only the major components of the liberated alkaloidal fractions has been made; in many cases this corresponds to the relatively solvent insoluble erysodine, erysopine and erysonine. The solvent soluble erysocine, erysovine and others were not always sought since they require other techniques of isolation and purification.

The new erysonine is unique in several respects. It has been isolated only from *E. costaricensis* and even then only from certain seed samples of this plant. Although its isolation from these samples was not difficult, it might escape isolation by these methods where small amounts of it exist in admixture with large amounts of erysodine and possibly erysopine. We believe, however, that it has not existed in any appreciable amounts in the other species so far examined. The samples Niehaus 9200 and 9364 of *E. costaricensis* yielded erysonine similarly, but sample Skutch 9740 did not yield erysonine after a very careful examination. However, it was found by Krukoff[7] that few other species, if any, showed such variations in certain botanical characters as did *E. costaricensis*, also that it likely hybridizes with *E. Berteroana* Urb.

Microanalyses have shown that erysonine has the empirical formula $C_{17}H_{19}NO_3$, possesses one methoxyl group and neither an N-methyl nor C-methyl group. Since it is soluble in dilute sodium hydroxide solution, one oxygen atom presumably exists in a phenolic hydroxyl group, and the third oxygen atom is probably in a hydroxyl group also.

Because of the considerable difficulties we have encountered in separating *Erythrina* alkaloids and in establishing their homogeneity, it seemed desirable to perform preliminary chromatographic analyses of erysonine to check its purity. Purified crystalline erysonine is sparingly soluble in most of the common solvents, and this factor restricted the chromatographic technique. However, experiments on chromatographing erysonine in morpholine, and in a mixture of chloroform and methanol as solvents over aluminum oxide did not yield a product with altered melting point or specific rotation.

Of the eryso- alkaloids, erysonine and erysopine are the least soluble in the alcohol solvents, and possess similar low solubilities. The specific rotations of these two alkaloids in 0.5% aqueous hydrochloric acid are so nearly identical that this constant would not be a good criterion in establishing the purity of either alkaloid. However, there is a difference of about 50° when the determination is made in morpholine and the presence of one as an impurity to the other might be indicated by the rotation in this solvent. Furthermore, this solvent dissolves both alkaloids readily at 25°.

Erysonine in aqueous solution as the hydrochloride caused the characteristic curare-like action when injected intralymphatically into frogs at a dose of 100 mg./kg. (calculated as the salt). It is not as highly active for curare-like action in the frog as certain other *Erythrina* alkaloids such as erythramine and erythraline.

As noted before,[3] we found again that the rate of hydrolysis of the combined alkaloids varies greatly. Erysodine was liberated so readily that a portion of it was found in the free alkaloidal fraction of *E. subumbrans*. Erysopine is liberated slowly and frequently appears only in the liberated fractions of the prolonged hydrolyses.

Reference to Table II, Parts A and B, reveals that the amounts of the liberated alkaloidal fractions generally exceed those of the free alkaloidal fractions.

Hypaphorine, as the hydrochloride, has been isolated for the first time from *E. crista-galli*, *E. costaricensis*, *E. Dominguezii*, *E. acanthocarpa*, *E. rubrinervia*, and *E. senegalensis*. In fact, hypa-

(6) Folkers and Unna, *J. Am. Pharm. Assoc.*, **28**, 1019 (1939).
(7) Krukoff, *Brittonia*, **3**, 317 (1939).

TABLE II

DATA ON THE ISOLATION OF ALKALOIDS FROM SPECIES OF ERYTHRINA

PART A. FREE ALKALOIDAL FRACTION

Line	Plant	Collectors' names and specimens numbers	Amount seeds, g.	Fatty fraction, %	Alcohol extractives, %	Free alkaloidal fraction, %	Hypaphorine hydrochloride,[g] %
1	*E. crista-galli* L.	Cabrera 9302	362.0	15.9	15.6	0.31[e]	
2	*E. crista-galli* L.	Diddell 9132	100.0	15.5	16.0[b]	.4[d]	2.1
3	*E. crista-galli* L.	Diddell 9132	200.0	15.0	14.7[b]	.4[d]	2.9
4	*E. costaricensis* Micheli	Niehaus 9200	50.0		18.2[a]	.67[d]	1.5
5	*E. costaricensis* Micheli	Niehaus 9364	677.0	13.2	15.8[a]	.35[e]	
6	*E. costaricensis* Micheli	Skutch 9740	589.0	18.5	13.5[a]	.27[e]	
7	*E. subumbrans* (Hassk.) Merr.	Holttum 9204/34, 801	685.0	14.1	22.7[a]	.32[e,k]	
8	*E. Dominguezii* Hassler	Schulz 9197/1569	152.0	11.8	25.2[a]	1.86[e]	0.7
9	*E. macrophylla* DC.	Armstrong 9442/52, 53	800.0	12.2	24.0[a]	0.22[e]	3.5
10	*E. acanthocarpa* E. Mey	Everitt 9198	100.0	17.9	19.8[b]	.13[e]	5.8
11	*E. rubrinervia* H. B. K.	Jaramillo 9181	50.0	11.4	15.2[a]	.2[d]	1.3
12	*E. senegalensis* DC.	Bur. Affair. 9202 Econ. Fr. Guin.	50.0	9.2	19.1[a]	.06[d]	3.1
13	*E. fusca* Lour.	Tamesis 9345	980.0	7.8	15.8[a]	.19[e]	[h]
14	*E. fusca* Lour.	Holttum 9256/21421	671.0	11.3	13.7[a]	.068[e]	[h]

PART B. LIBERATED ALKALOIDAL FRACTION

Line	Plant	Acid hydrolyses[c] First T	First Y	Second T	Second Y	Third T	Third Y	Total liberated alkaloidal fr.,[f] %	Alkalo
1	*E. crista-galli* L.	90	1.13	60	0.10			1.23	*j*
4	*E. costaricensis* Micheli	60	1.50					1.50	*o*
5	*E. costaricensis* Micheli	60	0.34	60	.13	60	0.12	0.59	*n*
6	*E. costaricensis* Micheli	180	0.45	60[i]	.22	60[i]	.09	0.76	*m*
7	*E. subumbrans* (Hassk.) Merr.	10	0.11	60	.69	120	.27	1.07	*l*
8	*E. Dominguezii* Hassler	10	3.5	20	.31			3.81	*p*
9	*E. macrophylla* DC.	10	0.25	20	.09	30	.49	0.89[r]	*q*
10	*E. acanthocarpa* E. Mey	5	0.61	60	1.03			1.64	*s*
11	*E. rubrinervia* H. B. K.	30	0.18					0.18	*t*
12	*E. senegalensis* DC.	105	1.34	120	0.09			1.43	*u*
13	*E. fusca* Lour.	10	0.52	20	0.14			0.66	*v*
14	*E. fusca* Lour.	45	0.16	60[i]	0.44			0.60	*w*

[a] Methanol was used. [b] Ethanol was used. [c] The free alkaloidal fraction was removed by the preferred procedure as described in paper IX. [d] The free alkaloidal fraction was removed by the alternative procedure as described in paper IX. [e] The hydrolyses were made on aqueous solutions acidified with hydrochloric acid to about *p*H 2-2.3; T = time in minutes, y = % yield of crude liberated bases after removal of the chloroform solvent. [f] The total yield of chloroform residues. [g] The hypaphorine was removed by the alternative procedure as described in paper IX. Further remarks on the isolation of hypaphorine are to be found in paper III. [h] Examination for hypaphorine was not made. [i] Hydrolysis was made at *p*H 1.

[j] **Erysopine and Erysodine from *E. crista-galli* L.**—The solution after the first hydrolysis was made alkaline with sodium bicarbonate, shaken with chloroform, and refrigerated overnight. By filtration, 2.404 g. of water and chloroform insoluble bases was obtained, m. p. 207–209°. Extraction of the aqueous solution ten times with chloroform yielded 1.708 g. of bases. The insoluble portion was dissolved in 500 ml. of ethanol by refluxing and distilled to incipient crystallization; yield, 1.337 g., m. p. 222–223°. A second recrystallization yielded 1.089 g. of m. p. 231° and the third recrystallization yielded 952 mg. of pure erysopine, m. p. 242–243°, $(\alpha)^{25}D$ +263, 40% glycerol and 60% ethanol, $(\alpha)^{25}D$ +276 (C = 18.413 mg./2.023 ml. 0.5% aqueous hydrochloric acid), $(\alpha)^{25}D$ +225 (C = 13.860 mg./2.023 ml. morpholine). The chloroform residue was treated with 1 ml. of ethanol and refrigerated overnight; 574 mg. of crystalline bases was obtained, m. p. 190–192°. One recrystallization yielded 470 mg. of m. p. 199–200°, and the second recrystallization yielded 259 mg. of pure erysodine, m. p. 200–201°, $(\alpha)^{25}D$ +248, ethanol. One-half of aqueous solution was hydrolyzed for the second time, but the chloroform extraction residue weighed only 178 mg. which gave only a few dark-colored crystals when treated with 0.5 ml. of ethanol.

[k] **Erysodine from Free Alkaloidal Fraction** of *E. subumbrans* (**Hassk.**) **Merr.**—It was discussed in paper IX[3] that even under the "preferred" method of extraction some liberated alkaloids might be introduced into the free alkaloidal fraction. This was true for erysodine in the free fractions of *E. abyssinica* Lam., and it is shown here for *E. subumbrans*. The 2.199 g. of crude free fraction (crude erythramine)[8] was shaken three hours with 50 ml. of 15% sodium hydroxide solution and extracted ten times to re-

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

move 1.2458 g. of crude erythramine. The alkaline solution was made acid, then alkaline with sodium bicarbonate and extracted with chloroform to yield 402 mg. of bases. When treated with 0.5 ml. of ethanol, 140 mg. of almost pure erysodine of m. p. (and mixed m. p.) 199–201° was obtained. Recrystallization from ethanol gave 105 mg. of pure erysodine, m. p. 200.5–201.5°, $(\alpha)^{25}D$ +245.

[l] **Erysodine and Erysopine from** *E. subumbrans* **(Hassk.) Merr.**—The 733 mg. of residue from the first hydrolysis was treated with 0.7 ml. of ethanol, and 162 mg. of crude erysodine of m. p. 196–198° was obtained. After eight chloroform extractions subsequent to the second hydrolysis, 837 mg. of erysopine separated and was filtered. It showed m. p. 238–240° (mixed m. p. 240–241°) and gave the green color test with ferric chloride. After five more extractions, all chloroform extracts were concentrated, etc., and 3.930 g. of bases was obtained. Treatment with 6 ml. of ethanol gave 2.133 g. of crude erysodine, m. p. 198–200°. After seven chloroform extractions subsequent to the third hydrolysis, 588 mg. of erysopine separated and was filtered. It showed m. p. 238–239° (mixed m. p. 239–240°) and gave the green color test with ferric chloride. Five more extractions gave 1.247 g. of bases which when treated with ethanol yielded 340 mg. of crude erysodine, m. p. 198–200°. All three crops of crude erysodine were combined and recrystallized twice from ethanol to give 1.693 g. of pure erysodine, m. p. 200–202°, $(\alpha)^{25}D$ +245.

[m] **Erysodine, and Erysopine from** *E. costaricensis* **Micheli (Skutch 9740).**—The chloroform residue of crude liberated alkaloids from the first hydrolysis of three hours weighed 2.673 g. It was triturated with 3 ml. of ethanol at 25°. The insoluble portion (A) was 684 mg. of m. p. 194–196° and the filtrate yielded 1.050 g. (B) of residue. The portion (A) was triturated with 3 ml. of hot ethanol and the insoluble portion (C) was 415 mg. of m. p. 198–200°; the filtrate yielded 150 mg. (D) of residue. The portion (C) was recrystallized twice from ethanol to yield 259 mg. of pure erysodine of m. p. 201–202° and $(\alpha)^{25}D$ +250. The residue (D) was extracted with 30 ml. of boiling ether, and 72 mg. of insoluble portion (F) of m. p. 200–202° and 46 mg. of a soluble crop (E) of m. p. 170–175–200° was obtained. The portion (F) was recrystallized once to give 49 mg. of pure erysodine of m. p. 200.5–201° and $(\alpha)^{25}D$ +248. The crop (E) was apparently erysocine and erysodine. The residue (B) was extracted with 35 ml. of boiling ether to give 422 mg. of crude material of m. p. 156–158° and 488 mg. of a soluble crop (G) of m. p. 143–156°. Two recrystallizations of (G) from ether yielded 203 mg. of material of m. p. 160–162° and $(\alpha)^{25}D$ +233, ethanol, corresponding to the previously described erysocine.[3] The second hydrolyzed solution, after adding sodium bicarbonate, was free of insoluble decomposition matter and on fifteen chloroform extractions, yielded 1.309 g. of residue of m. p. 192–194°. A first trituration with 3 ml. ethanol at 25° yielded 853 mg. of insoluble portion of m. p. 196–198°, and a second trituration with 3 ml. of hot ethanol yielded 542 mg. of insoluble portion of m. p. 198–199°. The latter, on crystallization from ethanol, yielded 446 mg. of pure erysodine, m. p. 200–201°, and $(\alpha)^{25}D$ +248. The liberated alkaloids of the third hydrolysis amounted to 510 mg. which gave the green color test for erysopine with ferric chloride. A trituration with 1 ml. of ethanol gave 81 mg. of insoluble material of m. p. 192–193° which on trituration with 1 ml. of hot ethanol gave material of m. p. 212–213°. Two recrystallizations of this product from ethanol gave 15 mg. of erysopine of m. p. 239–240° and $(\alpha)^{25}D$ +264, 40% glycerol and 60% ethanol. There was no evidence of erysonine in the products of any of these hydrolyses and no evidence of erysopine in the products of the first and second hydrolyses.

[n] **Erysonine and Erysodine from** *E. costaricensis* **Micheli (Niehaus 9364).**—The liberated bases from the three hydrolyses were combined after finding that each gave a positive color test for erysopine. After trituration with warm ethanol, 940 mg. of bases, m. p. 195–200° was obtained. One recrystallization of those bases from ethanol gave 440 mg., (A) m. p. 233–236°, which gave a negative color test for erysopine. The mother liquor gave 382 mg. of residue, m. p. 183–185°, (B). Recrystallization of (A) five more times from ethanol gave a product of constant melting point after the second crystallization. As for erysonine from Niehaus 9200, the melting point with decomposition of erysonine from this sample was difficult to ascertain and its determination was always checked against that of a sample from the previous crystallization. The average constants observed were 236–237° to 238–239°; $(\alpha)^{25}D$ +285–288°, 0.5% aqueous hydrochloric acid; $(\alpha)^{25}D$ +272, morpholine. The decomposition point of erysonine from Niehaus 9200 was in this range when compared with this sample. *Anal.* Calcd. for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.91; 1—OCH_3, 10.87. Found: C, 71.75; H, 6.78; N, 4.98; —OCH_3, 11.14. The soluble residue (B) was extracted with ether to yield 210 mg. of insoluble material, m. p. 190–195°. The latter was dissolved in 2% aqueous sodium hydroxide and extracted ten times with chloroform. The solvent residue, 92 mg., m. p. 198–200°, was recrystallized to yield erysodine, m. p. 200–202°, $(\alpha)^{25}D$ +245.

[o] **Erysonine from** *E. costaricensis* **Micheli (Niehaus 9200).**—The chloroform residue of the hydrolysis weighed 748 mg. and after trituration with 0.6 ml. of ethanol, 358 mg. of bases of m. p. 180–235° was obtained which gave a negative color test for erysopine. Four crystallizations from ethanol gave a base which had a constant melting point from the second crystallization; yield, 86 mg., m. p. 241–243° decompn.; $(\alpha)^{25}D$ +289, 0.5% aqueous hydrochloric acid. This base was recognized as being new and was named erysonine. It does not give a green color with ferric chloride solution. Its melting point is difficult to obtain because it melts with decomposition and the value varies with the rate of heating the bath. *Anal.* Calcd. for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.91; 1—OCH_3, 10.87. Found: C, 71.54, 71.60; H, 6.78, 6.77; N, 5.02; —OCH_3, 10.72; $=NCH_3$, none; $\equiv C-CH_3$, none.

[p] **Erysodine and Erysopine from** *E. Dominguezii* **Hassler.**—The crude bases of the first hydrolysis, 5.353 g., were triturated with ethanol to give 1.317 g. of bases, m. p. 197–199°, which after recrystallization from ethanol gave 1.011 g. of pure erysodine, m. p. and mixed m. p. 200–202°, $(\alpha)^{25}D$ +250. The second hydrolysis gave 473 mg. of gum bases which after trituration with 0.4 ml. of ethanol gave 24 mg. of crude erysopine, m. p. 215–216°, which gave the characteristic green color with ferric chloride.

[q] **Erysopine and Erysodine from** *E. macrophylla* **DC.**—The 2.0 g. of bases of the first hydrolysis yielded 41 mg. of erysopine, m. p. 242° on crystallization from ethanol. A second crop, 575 mg. of m. p. 198–199°, was triturated with ethanol and the soluble portion was twice recrystallized from ethanol to give 33 mg. of erysodine, m. p. 198–200°, $(\alpha)^{25}D$ +246. The 750 mg. of bases of second hydrolysis was recrystallized from ethanol to give 214 mg. of erysopine, m. p. 241–242°. The 539 mg. of bases of the third hydrolysis gave 53 mg. of erysopine, m. p. 241–242°, on crystallization from ethanol. During the chloroform extraction, 3.43 g. of erysopine, m. p. 241–242°, separated from the aqueous solution. Two crystallizations from ethanol did not alter the m. p. 241–242°, $(\alpha)^{25}D$ +264.

[r] A fourth hydrolysis of thirty minutes yielded 495 mg. of bases containing more erysopine.

[s] **Erysopine from** *E. acanthocarpa* **E. Mey.**—During the chloroform extraction after the first hydrolysis, crude erysopine separated from the solution; yield, 455 mg., m. p. 233–235°. The 156 mg. of chloroform residue yielded crude insoluble erysopine when triturated with ethanol. The second hydrolysis gave similar results. The erysopine which separated was 573 mg., m. p. 234–236°, and the chloroform residue of 458 mg. yielded crude erysopine. The combined erysopine was recrystallized once from ethanol to give 883 mg. of pure erysopine, m. p. 240–241°. A second crystallization after many months gave erysopine of $(\alpha)^{30}D$ +264°.

[t] **Erysopine from** *E. rubrinervia* **H. B. K.**—The 89 mg. of crude liberated alkaloids was triturated with 0.5 ml. of ethanol to give 29 mg. of erysopine, m. p. 240–242°, $(\alpha)^{25}D$ + 262°.

[u] **Erysodine and Erysopine from** *E. senegalensis* **DC.**—The 673 mg. of chloroform residue from the first hydrolysis gave 326 mg. of bases, m. p. 199.5–201°, which gave 244 mg. of pure erysodine after crystallization from ethanol; m. p. 202–204°, $(\alpha)^{25}D$ +247. The second hydrolysis gave 46 mg. of erysopine as shown by the green color test with ferric chloride. The erysopine was impure.

[v] **Erysopine and Erysodine from** *E. fusca* **Lour.**—The alkaline solution subsequent to the first hydrolysis was saturated with chloroform and allowed to stand many hours at 10°. When the insoluble erysopine, 4.948 g., m. p. 237–239°, had been filtered, the solution was extracted and 756 mg. of chloroform residue was obtained. The residue gave 182 mg. of erysodine containing a little erysopine, m. p. 197–198°, on trituration with 1 ml. of ethanol. Two recrystallizations gave erysodine of m. p. and mixed m. p. 199–201°. The second hydrolysis gave 1.011 g. of water insoluble erysopine, m. p. 238–240°, and 346 mg. of chloroform residue which contained erysopine. Recrystallization of such water insoluble erysopine from ethanol gave pure material of m. p. 240–241°. Erysopine could not be recrystallized satisfactorily from methanol since it decomposed slightly during the process.

[w] **Erysopine and Erysodine from** *E. fusca* **Lour.**—The first hydrolysis gave 616 mg. of insoluble crude erysopine (A), m. p. 216–217°, and 289 mg. of chloroform residue (B). Two recrystallizations of (A) from ethanol gave 298 mg. of pure erysopine, m. p. 239–240°, $(\alpha)^{25}D$ +265. Trituration and three crystallizations of the chloroform residue (B) yielded 10 mg. of pure erysopine. The second hydrolysis gave 1.86 g. of crude erysopine, m. p. 211–214°, which separated from the aqueous solution. The 1.085 g. of chloroform gum residue gave 195 mg. of base, m. p. 195–197° on ethanol trituration. Two crystallizations and separation of the soluble crop on the third crystallization gave 67 mg. of pure erysodine, m. p. 201–202°, $(\alpha)^{25}D$ +247.

phorine has been found so far in every species of *Erythrina* examined for this alkaloid.

The character of the new interesting free alkaloidal fractions of Table II, Part A, will be described in the future.

Experimental Part

General Remarks.—In order to conserve space, our voluminous experimental data are being concisely described. The data on the generalized part of the procedures have been recorded in Table II, Parts A and B. The actual details of the procedures were analogous to those of the experiments described in paper IX.[3] Reference to the General Remarks to the Experimental Part of paper IX[3] should also be made for additional information which is not described again here. The important details of this study, which cannot be tabulated satisfactorily, concern the fractional crystallizations of the liberated alkaloids and their identification. These data are carefully, although briefly, described in the form of expanded notes on Part B of Table II. For the hydrolyses, after removal of the free alkaloidal fraction, the aqueous solutions were acidified with hydrochloric acid to *p*H 2–2.5, except in a few cases where, as indicated in the notes, the solutions were acidified to *p*H 1. For exploratory work on unexamined species, successive hydrolyses have proved helpful in alkaloid separations because of the different rates of hydrolysis of the combined alkaloids. For preparative work on known species, a single prolonged hydrolysis can be made and the total mixed liberated alkaloids appropriately separated.

Chromatographic Analyses of Erysonine.—Because of the low solubility of erysonine in solvents at 25°, only two solvents could be used for the analysis of semi-micro amounts of the alkaloid. Morpholine was one and a 50–50 mixture of methanol and chloroform was the other solvent.

A solution was made of 93 mg. of erysonine (m. p. 236–237°; $(\alpha)D$ +288 (9.00 mg. in 10 ml. of 0.5% aqueous hydrochloric acid), +280 (11.663 mg. in 2.033 ml. of 0.5% aqueous hydrochloric acid)) in 10 ml. of morpholine and passed through a 15 × 1 cm. column of aluminum oxide Merck (according to Brockmann). The tube under ultraviolet light showed two prominent fluorescent bands. There was a light green fluorescent band at the top of 8 mm. width which appeared as a light brown band in daylight. It was the usual band that appears on top on chromatographing the eryso- alkaloids and appears to consist of decomposition products. The second band of 5 mm. width appeared 12 cm. from the top and showed a light yellow fluorescence. About 5 ml. of solvent came through which did not leave a residue on removal of the solvent. Development with 10 ml. of morpholine caused very little change in the appearance of the tube. The col-

lected solvent gave no residue. Development with another 10-ml. portion of morpholine caused the yellow band to appear fainter and 78 mg. of residue was obtained on distilling the collected solvent. Two crystallizations from ethanol yielded 10 mg. of erysonine of m. p. 238–239° (original erysonine observed simultaneously melted also at 238–239°) and $(\alpha)_D$ +280 (*c* 7.336 mg. in 2.033 ml. 0.5% aqueous hydrochloric acid).

A solution was made by dissolving 120 mg. of erysonine (same material as dissolved in morpholine) in 50 ml. of a 50–50 mixture of methanol and chloroform.

This solution was passed into a 30 × 1.9 cm. column of aluminum oxide Merck (according to Brockmann) without suction. No solvent passed through. The ends of the tube were stoppered and the tube was observed under ultraviolet light. There was a 1 mm. band on the very top of the green fluorescence which corresponds to a slight amount of decomposition products and this material was not recovered. There were six similar striations placed at approximately 4, 6, 10, 14.5, 20, and 25 cm. from the top which had a pale light yellow fluorescence under ultraviolet light. There was a thin brighter line which seemed to be near the edge of the advancing solvent line. On developing with 50 ml. of the same mixed solvents, the striations moved down about 1 cm. each and the collected solvent gave only 1 mg. of residue.

The adsorbent was separated into two portions under the ultraviolet light. All the fluorescent portions were combined and the non-fluorescent portions were combined. The top thin layer containing the decomposed material was discarded. Both portions were eluted by continuous hot extraction for eight hours with the same mixed solvent. After distillation of the solvent from the fluorescent portions, 30 mg. of residue was obtained which yielded 12 mg. of erysonine on crystallization from ethanol; m. p. 235–236°, $(\alpha)_D$ + 282 (*c* 9.685 mg. in 2.023 ml. of 0.5% aqueous hydrochloric acid). The solvent from the non-fluorescent portions yielded 65 mg. of residue after distillation. Recrystallization of this material from ethanol yielded 30 mg. of erysonine, m. p. 236–237, $(\alpha)_D$ + 279 (*c* 19.307 mg. in 2.033 ml. of 0.5% aqueous hydrochloric acid).

These two chromatographic analytical experiments did not yield erysonine of altered melting point or specific rotation when compared to the original crystallized material.

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Summary

The liberated alkaloidal fractions obtained from the seeds of nine species of *Erythrina* have been examined. Erysodine and erysopine were isolated in many cases. One new liberated alkaloid named erysonine was isolated from the seeds of one species.

Erysonine has the empirical formula $C_{17}H_{19}NO_3$. Certain preliminary facts about its constitution have been described. Erysonine possesses a curare-like action in frogs when administered by intralymphatic injection. The threshold dose is 100 mg./kg.

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The Synthesis of *dl*-3,5-Diiodo-4-(2′,4′-diiodo-3′-hydroxyphenoxy)-phenylalanine, a Physiologically Inactive Isomer of Thyroxine

BY CARL NIEMANN AND C. E. REDEMANN

Although the structure of the physiologically active *l*-thyroxine has been known for a number of years, there is little information as to how this amino acid performs its characteristic physiological function. Harington[1] and, more recently, Bovarnick, Bloch and Foster[2] have set forth the obligatory structural requirements, as far as they are known, for the development of thyroxine-like activity but offer no suggestion as to why these requirements are necessary. In order to extend our knowledge along these lines, it seemed of interest to us to synthesize an isomer of thyroxine in which the hydroxyl group in the second ring was shifted from position 4′, as in thyroxine, to position 3′. This compound, *dl*-3,5-diiodo-4-(2′,4′-diiodo-3′-hydroxyphenoxy)-phenylalanine (I), was prepared and when tested on rats was found

(1) C. R. Harington, *Fortschritte Chem. organ. Naturstoffe*, **2**, 103 (1939).

(2) M. Bovarnick, K. Bloch and G. L. Foster, THIS JOURNAL, **61**, 2472 (1939).