yielded 2.21 g. of **ethyl 2,5-dibromo-3,6-dihydroxyphenylacetate,** m. p. 125–126°. A second crop of this product weighing 0.39 g. and melting at 123–125° was obtained from the mother liquor. The total yield amounted to 40%. An analytical sample prepared by another recrystallization of the first crop melted at 126–127°.

Anal. Calcd. for $C_{10}H_{10}O_4Br$: Br, 45.17; OC_2H_5, 12.7. Found: Br, 45.03; OC_2H_5, 12.6.

Reaction of 2,6-Dibromobenzoquinone with Ketene Acetal.—When this quonone was heated with ketene acetal in dry xylene, only a trace of ethyl bromide was evolved, showing that the reaction does not proceed by replacement of bromine.

The quinone[13] (5.00 g.) was refluxed with 4.40 g. (2 equivalents) of ketene acetal in 100 ml. of dry benzene for twelve hours. Removal of the benzene and ethyl orthoacetate left a dark red resin. Vacuum sublimation of this resin at 170° and 1 mm. gave 0.75 g. of a light brown oil which failed to crystallize. It was hydrolyzed in 75% alcohol, and yielded an oily residue which also failed to crystallize. This residue was dissolved in 10 ml. of dioxane, 0.5 ml. of concentrated hydrochloric acid added and the solution evaporated to dryness. The residue was a black tar from which nothing could be sublimed at 1 mm. and below 190°.

Reaction of 2-Bromonaphthoquinone with Ketene Acetal. Xanthopurpurin Diethyl Ether (XX).—A mixture of 10.1 g. of 2-bromonaphthoquinone and 20.2 g. of ketene acetal was heated to 125° for sixteen hours. The ethyl bromide eliminated in this reaction amounted to 40% of the theoretical. On cooling the reaction mixture a solid separated which was filtered off and washed with 50 ml. of cold 95% alcohol. The dark green crystals which were somewhat gummy were recrystallized from 95% alcohol and gave 3.11 g. of yellow-green crystals. These were dissolved in 150 ml. of dry benzene and boiled with 0.1 g. of norite. The solution was filtered, evaporated to a volume of 25 ml. and allowed to crystallize. The yield of the bright yellow xanthopurpurin diethyl ether, m. p. 169–170°, was 2.24 g. A second crop of 0.36 g. of this compound having the same melting point was obtained from the mother liquor. The yield of the combined crops amounted to 20.6%. Lower yields (14%) were obtained when 5 equivalents of ketene acetal were used. The compound had the correct carbon, hydrogen, and ethoxyl content for xanthopurpurin diethyl ether. The melting point of a mixture of this product with an authentic sample of xanthopurpurin diethyl ether prepared by the method of Plath[14] from xanthopurpurin[15] was 169–170°.

Reaction of 2,3-Dibromonaphthoquinone with Ketene Acetal. Ethyl 3-Bromonaphthoquinon-2-ylacetate (XXI).—A solution of 5.0 g. of 2,3-dibromonaphthoquinone and 6.0 g. of ketene acetal in 100 ml. of benzene was refluxed for twelve hours. When solvent was distilled off, a crystalline residue, which was somewhat oily, remained. This residue was washed with a little cold alcohol and sublimed at 150° and 1 mm. The sublimate was recrystallized from a mixture of alcohol and water and gave 2.47 g. of ethyl 3-bromo-1,4-naphthoquinon-2-ylacetate, m. p. 122–123°. A second crop of crystals of this product weighing 0.49 g. and melting from 120–122° was obtained from the mother liquor. The combined yield was 57.6%. Analytically pure material, prepared by another vacuum sublimation of the first crop, melted at 124–125°.

Anal. Calcd. for $C_{14}H_{11}O_4Br$: Br, 24.7; OC_2H_5, 13.9. Found: Br, 25.0; OC_2H_5, 13.9.

(13) Heinichen, *Ann.*, **253**, 285 (1889).

(14) Plath, *Ber.*, **9**, 1205 (1876).

Summary

The condensation product from ketene acetal and benzoquinone is shown to be 2-ethoxy-5-hydroxycoumarone instead of 7-ethoxy-2,5-diketobicyclo[4,2,0]octadiene-3,6 as previously reported.

Xyloquinones and 1,4-naphthoquinone are much less reactive than benzoquinone toward ketene acetal. The temperatures necessary to produce reaction appear to polymerize most of the initial reaction products so that only small yields of coumarones corresponding to the one obtained with benzoquinone are isolated. Duroquinone does not react with ketene acetal.

Bromoquinones are much more reactive toward the acetal than are the methyl-substituted quinones. With bromobenzoquinones the reaction takes place at one of the unsubstituted ring carbons. With the bromonaphthoquinones a bromine substituent is replaced with the evolution of ethyl bromide; 2-bromonaphthoquinone yields xanthopurpurin diethyl ether and 2,3-dibromonaphthoquinone yields ethyl 3-bromo-1,4-naphthoquinon-2-ylacetate.

(15) Friedlander, "Fortschritte der Teerfarbenfabrikation," Vol. 9, p. 691, Julius Springer, Berlin, 1911.

MADISON, WISCONSIN RECEIVED APRIL 20, 1944

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

Erythrina Alkaloids. XIV. Isolation and Characterization of Erysothiovine and Erysothiopine, New Alkaloids Containing Sulfur[1a]

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

The new alkaloids,[1b] erythramine, erythraline and erythratine, which were isolated from seeds of various species of *Erythrina* have been designated free alkaloids because they appear to exist in the seeds as free organic ammonium bases or salts, as indicated by the technique used in their isolation. These free alkaloids correspond to the well-known alkaloids isolated from many different families of plants. It is characteristic of many such alkaloids that they can be extracted from alkaline aqueous concentrates by certain immiscible organic solvents.

During the study and extraction[2] of the crude free alkaloidal fractions from *Erythrina glauca* Willd. and *Erythrina berteroana* Urb., it was found that after these fractions had been removed completely, the residual aqueous extracts were still very potent, as shown by the biological assays with frogs for curare-like action. For these two

(1a) Original manuscript received November 8, 1943.

(1b) Folkers and Koniuszy, THIS JOURNAL, **61**, 1232 (1939); *ibid.*, **62**, 436 (1940).

(2) Folkers and Koniuszy, *ibid.*, **62**, 1677 (1940).

and many other species of *Erythrina*, the physiological activities and the amounts of the isolated free alkaloidal fractions did not correspond to the original threshold doses of the extracts as determined by the biological assays. In other words, the threshold dose was frequently a measure of a second unknown active fraction, which was more potent or present in greater amount. After considering first that a glyco-alkaloidal fraction which was unextractable by an immiscible solvent might be present, suitable extracts from several species of *Erythrina* were exhausted of the free alkaloidal fraction, acidified with hydrochloric acid, and refluxed. After cooling, treating with sodium bicarbonate, and extracting with chloroform, a new fraction of alkaloidal bases was obtained. The residual aqueous solution, properly adjusted in *p*H, showed a corresponding drop in paralysis potency, and the new fraction showed paralysis activity. This new fraction was designated the liberated alkaloidal fraction, and from such fractions of many species of *Erythrina*, erysodine,[2] erysopine,[2] erysovine[2] and erysonine[3] were isolated. Since each of these alkaloids has a phenolic hydroxyl group, and since erysodine and erysovine possess no other free functional group, it was concluded that this group was formed in the hydrolytic reaction. Erythramine[4] and erythraline[4] do not possess any hydroxyl group, and erythratine[5] does not possess a phenolic hydroxyl group; hence, they cannot be combined similarly. Although acid rather than alkaline hydrolyses were found preferable and could be interpreted to indicate glyco-alkaloids, the structure of the compounds eventually isolated did not agree with this supposition.

Starting with extracts exhausted of the free alkaloids, exploratory experiments were made to isolate these alkaloids in their combined state. Lead acetate precipitated considerable active material from an extract of *Erythrina sandwicensis* Deg. Other procedures such as acetylation with pyridine and acetic anhydride, fractionations with organic solvents, ammonium sulfate additions, and precipitations with phosphotungstic acid were also explored. Although very potent preparations were obtained, they were frequently contaminated with hypaphorine, the complete separation of which was restricted by the properties of the betaine and the solubility behavior of its salts.

In the meantime, it was found that when rather concentrated aqueous solutions of the typical alcohol extractives were refrigerated for several weeks, a crop of crystals slowly developed in the thick liquor. Examination of these crystals as obtained from *Erythrina glauca* Willd. showed that recrystallization readily gave a compound of constant melting point and specific rotation. Microanalyses disclosed the presence of sulfur and a composition in agreement with the empirical formula, $C_{20}H_{23}NO_7S\cdot 2H_2O$. The anhydrous alkaloid was obtained by appropriate drying *in vacuo*.

When the acid hydrolysis procedure, which was used on the extracts to obtain the liberated alkaloidal fraction, was applied to this new crystalline substance, erysovine was obtained. In order to correlate the names, the combining form thio was introduced, and this combined alkaloid was named erysothiovine. The hydrolysis equation may be written as follows

$$\underset{\text{(erysothiovine)}}{C_{20}H_{23}NO_7S} + H_2O \xrightarrow{H^+} \underset{\text{(erysovine)}}{C_{18}H_{21}NO_3} + C_2H_4O_6S$$

The compound $C_2H_4O_6S$ was believed to be sulfoacetic acid, $HO_2CCH_2SO_3H$. This belief was confirmed by its isolation from a hydrolysis solution of erysothiovine as a crystalline aniline salt melting at 187–189°,[6] which was identical with a sample of this salt prepared synthetically.

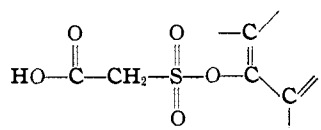
Erysothiovine was isolated similarly from the seeds of *Erythrina pallida* Britton and Rose and *Erythrina Poeppigiana* (Walp.) O. F. Cook.

Another crystalline combined alkaloid, which was more soluble, was isolated from the extract of *Erythrina glauca* Willd. It contained sulfur also, and the microanalytical data were in agreement with the formula, $C_{19}H_{21}NO_7S\cdot H_2O$. Appropriate drying *in vacuo* again yielded the anhydrous alkaloid. Acid hydrolysis of this substance gave erysopine, and the following equation is in agreement with the formation of sulfoacetic acid.

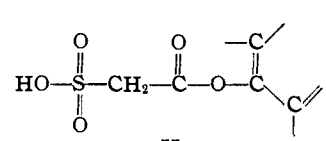
$$\underset{\text{(erysothiopine)}}{C_{19}H_{21}NO_7S} + H_2O \xrightarrow{H^+} \underset{\text{(erysopine)}}{C_{17}H_{19}NO_3} + C_2H_4O_6S$$

This combined alkaloid was named erysothiopine.

These combined alkaloids are obviously esters of sulfoacetic acid and erysovine, erysopine, etc. They are probably sulfonic esters, I, and not carboxylic esters, II, involving a phenolic hydroxyl



I



II

group of the alkaloid moiety, because aqueous solutions of sulfoacetic acid give water insoluble lead or barium salts when treated with solutions of lead acetate or barium chloride, whereas erysothiovine and erysothiopine (1.8% fresh aqueous solutions at 25°) are not precipitated from solution by lead acetate or barium chloride solutions. After warming acidified solutions of erysothiovine

(3) Folkers, Shavel and Koniuszy, THIS JOURNAL, **63**, 1544 (1941).
(4) Folkers and Koniuszy, *ibid.*, **61**, 3053 (1939); **62**, 1673 (1940).
(5) Folkers, Koniuszy and Shavel, *ibid.*, **64**, 2146 (1942).
(6) Stillich, *J. prakt. Chem.*, **73**, 538 (1906); **74**, 51 (1906).

and erysothiopine, precipitation of insoluble salts does occur when lead acetate or barium chloride solutions are added, but this behavior is due to sulfoacetic acid which is formed by hydrolysis. It is interesting that, although erysopine possesses two phenolic hydroxyl groups, only one is esterified in this way.

It appeared likely that the one phenolic hydroxyl group of erysovine could react with the sulfonyl chloride, $HO_2CCH_2SO_2Cl$, for the possible resynthesis of erysothiovine and proof of structure I or II. An attempt to prepare this sulfonyl chloride, which involved the chlorination of the isothiourea salt from chloroacetic acid and thiourea, led to an unexpected violent explosion,[7] and resynthesis by this route was abandoned.

Past studies[2,3] showed that the hydrolyses which gave the liberated eryso- alkaloids had quite different rates of reaction. Thus, some erysodine was found in the free alkaloidal fraction of *E. subumbrans* (Hassk.) Merrill, *E. abyssinica* Lam., and *E. sandwicensis* Deg., even though this latter fraction was isolated under conditions at 25° carefully designed to avoid hydrolysis. Erysopine was frequently liberated so slowly that it appeared only in those liberated fractions produced after prolonged periods of refluxing. Successive hydrolyses for various periods of time based upon these different rates of liberation were utilized to aid isolation of the individual eryso- alkaloids. Although attempts were made to isolate a similar sulfoacetic acid ester of erysodine, particularly from *E. sandwicensis* Deg. which once yielded[2] 2% of pure erysodine, it was not obtained. Furthermore, "erysothiodine" was not obtained from the three other species which gave erysothiovine, although erysodine was isolated from the liberated alkaloidal fractions of each species. Perhaps the solubility of "erysothiodine" in water is too high for isolation of it by the technique tried. It might be isolated by other methods.

It appears possible that the free acid group of the ester alkaloid, I, is esterified with another molecule and hydrolysis of this ester linkage during the storage periods for crystallization precedes and is the controlling step for the slow crystallization of the sulfoacetic acid alkaloid esters.

Erysothiovine is weakly basic, as shown by its tendency to crystallize from aqueous solutions acidified with hydrochloric acid. Consequently aqueous solutions of it were best prepared by adding sodium hydroxide to form the sodium salt.

The curare-like action of these alkaloids was studied by Dr. Klaus Unna of the Merck Institute for Therapeutic Research, to whom we are indebted for the data in Table I. This table lists the minimum doses of the combined and liberated alkaloids which, upon intralymphatic injection, produce curare-like paralysis in frogs. Erysovine is the most potent liberated alkaloid, and the combined alkaloids are more potent than their corresponding liberated alkaloids. Further studies on the pharmacologic action of these alkaloids are published elsewhere.[8]

(7) Folkers, Russell and Bost, THIS JOURNAL, **63**, 3530 (1941).

TABLE I

THRESHOLD DOSE LEVELS FOR CURARE ACTION

Alkaloid	mg./kg. frog
Erysonine (as hydrochloride in solution)	100[3]
Erysodine (as hydrochloride in solution)	15
Erysopine (as hydrochloride in solution)	4
Erysothiopine (as sodium salt in solution)	1
Erysovine (as sodium salt in solution)	3
Erysothiovine (as sodium salt in solution)	1

Such alkaloidal esters of sulfoacetic acid do not appear to have been isolated from plants and described heretofore.

Experimental Part

Isolation of Erysothiovine and Erysothiopine from Erythrina glauca Willd.—A 2-kg. quantity of ground seeds of *Erythrina glauca* Willd. (Wortley 9242)[9] was extracted with petroleum ether and then with methanol by the technique already described[1] for *Erythrina sandwicensis* Deg. The residue obtained after distillation of the methanol was dissolved in 1 liter of water and freed of residual fatty oil droplets by centrifuging. The aqueous solution was covered with a thin layer of petroleum ether and allowed to stand at 25° for four months. After this time, 962 mg. of crystals was obtained by filtration; m. p. 183–186° with dec. After two recrystallizations from water, short white crystals of constant behavior in respect to the following properties were obtained: m. p. 187°, $[\alpha]^{25}D$ +208°, *C*, 0.359, ethanol. When these crystals were dried at 25° *in vacuo* for an hour, the subsequent analytical data indicated a dihydrate.

Anal. Calcd. for $C_{20}H_{23}NO_7S\cdot 2H_2O$: C, 52.51; H, 5.94; N, 3.06. Found: C, 52.55, 52.79; H, 5.83, 5.63; N, 3.16.

Drying at 100° *in vacuo* removed the water incompletely as judged by the carbon content. A sample dried to constant weight at 140° *in vacuo* gave the following analytical data which correspond to the anhydrous material.

Anal. Calcd. for $C_{20}H_{23}NO_7S$: C, 57.01; H, 5.50; N, 3.32; S, 7.59. Found: C, 57.17; H, 5.57; N, 3.57; S, 7.38.

This new sulfur-containing alkaloid was named erysothiovine.

One-third of the above aqueous solution was refrigerated again for forty days. After this time, 300 mg. of crystals melting at 196–197° was obtained. When a portion of these crystals was recrystallized from 50% ethanol, crystals of erysodine (m. p. 202–204°) were obtained. When another portion was recrystallized from 95% ethanol, the crystalline product melted at 167–168° and contained sulfur. The small amount of erysodine present in the crude crystals is less soluble in 50% ethanol and thus crystallizes first. The erysodine is quite soluble in 95% ethanol and so the remainder of the crude product was recrystallized from 95% ethanol and, after a second crystallization, material of constant melting point was obtained; m. p. 168–169°; yield 248 mg.; $[\alpha]^{25}D$ +194°, *C*, 0.103, ethanol. A sample was dried for two hours at 140° *in vacuo* before analysis. The analytical data were satisfactory for a monohydrate of a new alkaloid which was named erysothiopine.

(8) Unna, *J. Pharmacol.*, **80**, 39 (1944); **80**, 53 (1944).

(9) The collectors' names and specimen numbers were assigned by Mr. B. A. Krukoff to the botanical specimens taken from the same plants as the seeds. See Krukoff, *Brittonia*, **3**, 205 (1939); *Am. J. Botany*, **28**, 683 (1941).

Anal. Calcd. for $C_{19}H_{21}NO_7S \cdot H_2O$: C, 53.64; H, 5.44. Found: C, 53.32; H, 5.50.

When erysothiopine was crystallized from 95% ethanol and air-dried, the carbon and hydrogen values were indicative of a dihydrate. This dihydrate appeared to lose one molecule of water rather readily.

From about two gallons of aqueous solution containing dissolved methanol residue prepared as described above, 6.5 g. of crude sulfur containing alkaloidal material was obtained; m. p. 182–183°. Recrystallization of 6.188 g. of this material from water yielded 4.818 g. of crystals; m. p. 166–168°, $[\alpha]^{25}D$ +187°. A second crystallization gave 4.067 g. of pure erysothiopine; m. p. 168–169°, $[\alpha]^{25}D$ +193°, *C*, 0.183, ethanol. A sample was pulverized and dried to constant weight during three hours at 100° *in vacuo*. This product was anhydrous.

Anal. Calcd. for $C_{19}H_{21}NO_7S$: C, 56.01; H, 5.19; N, 3.44; S, 7.87. Found: C, 55.98; H, 5.19; N, 3.31; S, 7.90.

Hydrolysis of Erysothiovine to Erysovine and Sulfoacetic Acid.—A sample (301 mg.) of pure erysothiovine was dissolved in 50 ml. of 2% hydrochloric acid and the solution refluxed fifteen minutes. After cooling, the acid solution was extracted five times with chloroform, but no material was extracted. The solution was made alkaline with sodium bicarbonate and extracted twelve times with chloroform. Distillation of the chloroform *in vacuo* left 178 mg. of a colorless brittle gum which was crystallized from ether. The crystalline erysovine which was obtained melted at 177° and did not depress the melting point of a reference sample of erysovine which had been isolated directly from a liberated alkaloid fraction.

A sample (129 mg.) of erysothiovine was dissolved in 1% aqueous sulfuric acid solution, and after refluxing for fifteen minutes, the cooled solution was treated with barium hydroxide solution. The barium sulfate was filtered and the filtrate was concentrated to a volume of 15 ml. and treated with a slight excess of aniline sulfate. The precipitate of barium sulfate was removed and the filtrate was concentrated to dryness. The residue was treated with 25 ml. of absolute ethanol and the mixture was filtered. Refrigeration of the ethanol filtrate for twelve hours yielded 22.9 mg. of crystals; m. p. 187–189°. Two recrystallizations of the product from ethanol did not alter the melting point of this crystalline aniline salt of sulfoacetic acid. There was no depression on a mixed melting point determination with the corresponding aniline salt from synthetic sulfoacetic acid made as described below.

Anal. Calcd. for $C_{14}H_{16}N_2O_4S$: C, 54.59; H, 5.23. Found: C, 54.23; H, 5.37.

Preparation of Sulfoacetic Acid.—A mixture of 50 g. of chloroacetic acid dissolved in 300 ml. of water, 76 g. of sodium carbonate decahydrate, and 134 g. of sodium sulfite was heated to the boiling point for twenty minutes. A hot solution of 130 g. of barium carbonate in 200 ml. of water was added, and the barium salt was filtered. After cooling the filtrate, crystals slowly formed. The solution was filtered again; yield, 5.7 g. of crystals. Concentration of the filtrate *in vacuo* gave more crystals; yield, 74.5 g. The aniline salt made from the first crop of the barium salt of sulfoacetic acid (5.7 g.) and aniline sulfate melted at 187–189° after purification from alcohol as described by Stillich.[9] This salt was difficult to crystallize.

Anal. Calcd. for $C_{14}H_{16}N_2O_4S$: C, 54.59; H, 5.23. Found: C, 54.70; H, 5.67.

A salt of sulfapyridine with sulfoacetic acid crystallized better. It was made by dissolving the components in 95% ethanol at 75°. The ethanol was distilled and the residue was dissolved in water. After filtering a little insoluble sulfapyridine, a crop of crystals (m. p. 160–161°) was obtained. Two recrystallizations of this material from ethanol yielded a product of constant melting point (m. p. 162–163°). It was dried at 100° for twenty minutes *in vacuo* before analysis.

Anal. Calcd. for $C_{24}H_{26}N_6O_9S_3 \cdot 3H_2O$: C, 41.61; H, 4.65. Found: C, 41.68; H, 4.87.

This salt was very soluble (30% solution) in hot water, and on cooling sulfapyridine (m. p. 189–190°) separated.

Isolation of Erysothiovine from *Erythrina pallida* Britton and Rose.—A quantity (300 g.) of ground seeds of *Erythrina pallida* Britton and Rose (Wortley 9257) was extracted with petroleum ether to remove the fatty fraction and with methanol to remove the alcohol extractives. The 47 g. of methanol residue was dissolved in 75 ml. of water and, after adding a thin layer of petroleum ether, was refrigerated. After a month, 22 mg. of crystalline material was collected by filtration through a cloth bag with suction. It was crude erysothiovine which melted at 181–183° and showed $[\alpha]^{25}D$ +207°. After ten months of refrigeration, a second crop of 540 mg. of crystals was obtained; m. p. 186–187°. After two recrystallizations from water with the aid of Norite for the first recrystallization, 495 mg. of pure white crystalline erysothiovine was obtained; m. p. 186–187°, mixed m. p. 186–187°, $[\alpha]^{25}D$ +208°, *C*, 0.186, ethanol.

Isolation of Erysothiovine from *Erythrina Poeppigiana* (Walp.) O. F. Cook.—A quantity (13.2 kg.) of ground seeds of *Erythrina Poeppigiana* (Walp.) O. F. Cook (Wortley 9241) was extracted with petroleum ether and then with methanol. The methanol residue (2819 g.) was dissolved in water and the solution was diluted to *ca.* 4600 ml. After covering the solution with a thin layer of petroleum ether, it was refrigerated. After a month, the long needle crystals were collected by filtering the thick green liquor through a linen bag. The crystals were washed with water and then acetone; yield 9.5 g.; m. p. 180–181°, $[\alpha]^{25}D$ +206°. Two recrystallizations from water gave pure erysothiovine of m. p. 186–187° and $[\alpha]^{25}D$ +208°.

In a pilot plant experiment, a batch (68 lb.) of ground seeds of *E. Poeppigiana* (Wortley 9241) was extracted with petroleum ether for removing the fatty fraction and then was extracted twice with refluxing ethanol. The ethanol filtrate was concentrated to dryness and the residue was dissolved in two gallons of water. This solution was freed of residual fatty materials by extracting with chloroform until the solvent was colorless. After refrigeration, 10.9 g. of fairly pure erysothiovine was eventually obtained; m. p. 181–183°. One recrystallization from water gave 8.1 g. of pure erysothiovine; m. p. 185–186°, $[\alpha]^{25}D$ +208°, *C*, 0.204, ethanol. A sample was dried in a pig[10] for three hours at 100° before analysis.

Anal. Calcd. for $C_{20}H_{23}NO_7S$: C, 57.01; H, 5.50; N, 3.32; S, 7.59. Found: C, 57.26, 57.12; H, 5.91, 5.54; N, 3.70, 3.69; S, 7.34.

Hydrolysis of Erysothiopine to Erysopine.—In this case, an attempt to isolate sulfoacetic acid was not made. A sample (87 mg.) of erysothiopine was dissolved in 25 ml. of 1% hydrochloric acid solution and the solution was refluxed fourteen minutes. The cooled solution was made alkaline with sodium bicarbonate and extracted twenty times with chloroform. Distillation of the extracts left 25 mg. of residue which melted at 238°. Recrystallization of it from ethanol gave a product which melted at 240–241° and this did not depress the melting point of pure erysopine. The specific rotation in glycerol and alcohol was also in agreement,[2] $[\alpha]^{25}D$ +264°. It also gave the characteristic green color with ferric chloride solution.

Acknowledgment.—We wish to express our appreciation to Mr. B. A. Krukoff of The New York Botanical Garden for obtaining the plant materials, for determination of specimens, and for advice on botanical matters. We are indebted to the people who aided in the collection of plant material for chemical examination. The microanalyses by Messrs. D. F. Hayman, W. Reiss, and H. S. Clark are gratefully acknowledged.

Summary

Studies on the combined alkaloidal fractions of several species of *Erythrina* led to the isolation and

(10) D. F. Hayman, *Ind. Eng. Chem., Anal. Ed.*, **10**, 55 (1938).

characterization of two new crystalline compounds containing sulfur. Microanalytical data showed that one compound had the formula, $C_{20}H_{23}NO_7S$, and the other, $C_{19}H_{21}NO_7S$. They yielded erysovine ($C_{18}H_{21}NO_3$) and erysopine ($C_{17}H_{19}NO_3$), respectively, on hydrolysis. For correlation of names and to designate the sulfur atom present, they were named erysothiovine and erysothiopine. Since the hydrolytic reaction yielded one mole of sulfoacetic acid in each case, erysothiovine and erysothiopine are alkaloidal esters of sulfoacetic acid with erysovine and erysopine. Apparently, they are sulfonic esters.

Erysothiovine and erysothiopine are highly active for curare-like paralysis in frogs and they are three to four times more active than the corresponding alkaloids erysovine and erysopine.

RAHWAY, NEW JERSEY RECEIVED APRIL 15, 1944

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. VI

BY F. F. BLICKE AND R. F. FELDKAMP[1,2]

It has been well established, during the last ten years, that basic-alkyl esters of certain diaryl-, diaralkyl-, arylcycloalkyl- and arylalkyl-acetic acids are effective agents for relief of spasms of the gastrointestinal tract. Many of these esters also produce local anesthesia and mydriasis when applied to the cornea.

Since β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin) is an effective spasmolytic, it was of interest to prepare other esters which contained two phenyl nuclei in the acyl radical. Obviously, esters of *p*-xenylacetic and of α-naphthylacetic acid represent such compounds. Esters of the former acid were described previously,[3] and this publication deals with esters of the latter type.

Incidentally, basic-alkyl esters of diphenylacetic acid which contain an *o,o'*-bridge, that is, esters of fluorene-9-carboxylic acid, have been shown to be active antispasmodics.[4]

Although α-naphthylacetic acid is analogous to diphenylacetic acid in that it contains two phenyl nuclei, it is unlike the latter inasmuch as it is a mono- instead of a disubstituted acid. Since the most active antispasmodics are esters of disubstituted acetic acids, and since β-diethyl-aminoethyl phenylpropylacetate has been shown to be a potent product,[5] we prepared also esters of α-naphthylalkylacetic acids in which the alkyl groups were represented by methyl and ethyl radicals. In addition, a few esters of α-naphthylphenylacetic acid were synthesized.

All esters were isolated in the form of crystalline hydrochlorides; attempts to obtain esters of α-naphthylpropyl- and α-naphthylbutylacetic acid as crystalline hydrochlorides were unsuccessful.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by R. F. Feldkamp in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

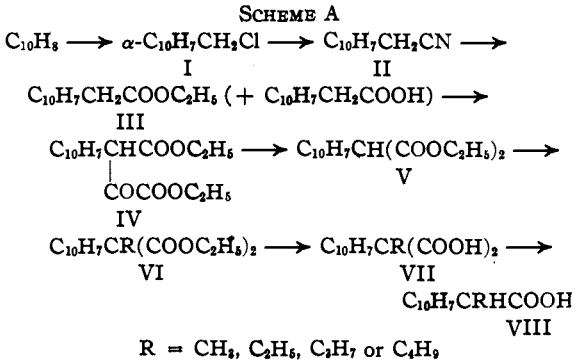
(3) Blicke and Grier, THIS JOURNAL, **65**, 1725 (1943).

(4) Burtner and Cusic, *ibid.*, **65**, 262 (1943); Lehmann and Knoefel, *J. Pharmacol. Exp. Therapy*, **74**, 274 (1942).

(5) Halpern, *Compt. rend. soc. biol.*, **126**, 678 (1937); *Arch. intern. pharmacodynamie*, **59**, 149 (1938).

The α-naphthylalkylacetic acids, required for the preparation of the esters, were synthesized according to schemes A and B. Only α-naphthylmethylacetic acid had been described hitherto. It was obtained by Tiffeneau and Daudel[6] by oxidation of α-naphthylmethylacetaldehyde.

SCHEME A



The conversion of naphthalene, by chloromethylation, into α-naphthylmethyl chloride (I), and of the latter into α-naphthylmethyl cyanide (II), requires no comments. When the cyanide was boiled with alcohol and sulfuric acid, ethyl α-naphthylacetate (III) was obtained; enough α-naphthylacetic acid for our purpose was also formed as a by-product so that it was not necessary to prepare this acid by a separate process. The acetate (III) reacted with ethyl oxalate and sodium ethylate to yield ethyl ethoxalyl-α-naphthylacetate (IV), and expulsion of carbon monoxide from the latter yielded diethyl α-naphthylmalonate (V). Alkyl groups were introduced in the usual manner to form diethyl α-naphthylalkylmalonates (VI). Hydrolysis of the esters, and partial decarboxylation of the acids yielded successively compounds of types VII and VIII.

The procedure indicated by scheme B was employed for the preparation of α-naphthylphenylacetic acid; we found that α-naphthylpropyl- and α-naphthylbutylacetic acid also can be synthesized satisfactorily by this method.

(6) Tiffeneau and Daudel, *Compt. rend.*, **147**, 679 (1908).