TECHNICAL PAPERS

The Conversion of β-Erythroidine to Derivatives of the Desmethoxy Series and Some Pharmacological Properties of Apo-β-Erythroidine[1, 2]

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β-Erythroidine differs from almost all other peripheral curariform agents in that it is much less effective when employed as the quaternary ammonium salt than when employed as the tertiary amine hydrochloride (*11*). Inasmuch as it is generally thought that the quaternary ammonium ion is very important in conferring curariform activity (*4*), the structural unit responsible for the curariform activity of β-erythroidine must, therefore, be of a different type from that of the usual curariform agent. We have made some preliminary investigations of β-erythroidine in the hope of establishing some relationship between structure and activity, and it is the purpose of this note to report the discovery of some new derivatives of β-erythroidine and to describe some of the unusual pharmacological properties of one of these derivatives, apo-β-erythroidine.

β-Erythroidine was first isolated and characterized by Folkers and Major (*8*). Following this excellent work, Folkers and Koniuszy (*6*) in 1939 and Folkers, Koniuszy, and Shavel (*7*) in 1941 reported on some chemical studies of β-erythroidine. As yet, no experimental details of this work have been published, and it is fair to say that the structure of β-erythroidine is still largely unknown.

In 1946 Dietz and Folkers (*5*) reported a spectrophotometric method of analysis for β-erythroidine based on the fact that the alkaloid, after treatment with sulfuric acid, gives a purple color with ferric chloride. We have investigated further the action of acids on β-erythroidine and have found that, depending on the conditions employed, any one of three different isomeric derivatives of β-erythroidine may be obtained. The conversion of β-erythroidine to these derivatives was accomplished by the following procedures.

When β-erythroidine ($C_{16}H_{19}NO_3$) was treated with hydrogen fluoride at room temperature there was obtained, after isolation and purification, a white, crystalline solid, mp 108–109° C, having the empirical formula, $C_{15}H_{15}NO_2$ (*Analysis*: Calculated for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; found: C, 74.74; H, 6.06). This product differs from β-erythroidine by the elements of methanol (CH_4O), and it would appear to have been formed by the simple loss of a methoxyl group with introduction of a double bond. In support of this view β-erythroidine was found to contain one methoxyl group (*Analysis*: Calculated for $C_{16}H_{19}NO_3$: 1-OCH_3, 11.35; found: OCH_3, 11.10) whereas the product from treatment of β-erythroidine with hydrogen fluoride was found to contain no methoxyl groups. Therefore, we have named this product, desmethoxy-β-erythroidine. Desmethoxy-β-erythroidine does not give a color with ferric chloride.

On the other hand, when β-erythroidine was heated to 120° C with either phosphoric or sulfuric acid, the product isolated from the reaction mixture after this more drastic treatment was a solid, which, after crystallization from ethanol, melted at 132–132.5° C. This compound was shown (*Analysis*: found: C, 74.94; H, 6.27) to be isomeric with desmethoxy-β-erythroidine, but it has quite different properties and gives a violet color with ferric chloride. We have designated this compound, therefore, as apo-β-erythroidine.

Some idea of the relationship of desmethoxy-β-erythroidine to apo-β-erythroidine was obtained when it was found that phosphoric acid at 80° C converted β-erythroidine to desmethoxy-β-erythroidine and that desmethoxy-β-erythroidine, in turn, was converted by phosphoric acid at 120° C to apo-β-erythroidine. It appears that the conversion of β-erythroidine to apo-β-erythroidine involves rearrangement as well as the loss of a methoxyl group.

Attempts to purify apo-β-erythroidine by chromatography led to still another product. This new product, mp 146–147° C, although isomeric with apo-β-erythroidine and desmethoxy-β-erythroidine (*Analysis*: found: C, 74.52, 74.81; H, 6.20, 6.39) has quite different spectra and properties from either of them. For reference it has been named iso-apo-β-erythroidine. The nature of the structural relationships of these three desmethoxy derivatives of β-erythroidine is of considerable interest and will be discussed in fuller detail elsewhere.

Desmethoxy-β-erythroidine, apo-β-erythroidine, and iso-apo-β-erythroidine have been tested for pharmacological activity, and although desmethoxy-β-erythroidine and iso-apo-β-erythroidine presented little of interest, apo-β-erythroidine showed quite unusual properties.

An intraperitoneal injection of apo-β-erythroidine to mice in doses of 150 mg per kg caused flaccid paralysis and loss of postural reflexes. The hind legs and posterior half of the body became affected first and remained paralyzed longer than the front limbs and neck muscles. During paralysis respiration remained adequate but was decreased in rate and increased in depth. Faradic stimulation of the sciatic nerve caused contraction of the paralyzed limbs. Paralysis was not preceded by excitation and was followed by complete recovery of muscular power.

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The paralyzing effect of apo-β-erythroidine was similar to that observed after administration of benzimidazole

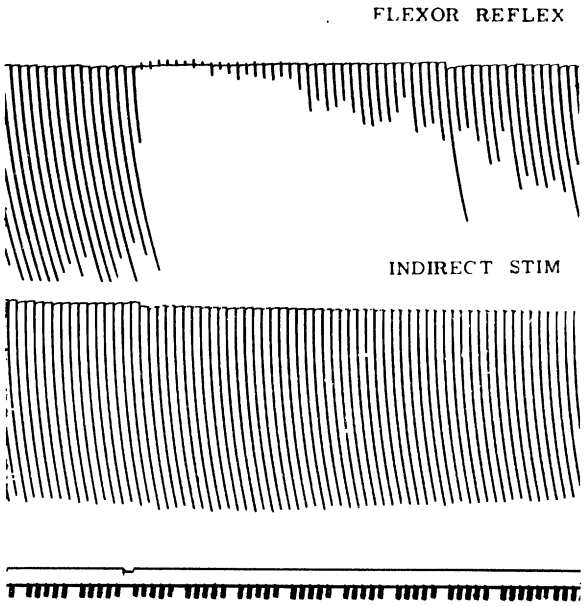

FIG. 1. Effect of apo-β-erythroidine on the flexor reflex and indirect excitability of the muscle. Tracing from above downwards: 1) flexor reflex; 2) stimulation of gastrocnemius muscle through its nerve; 3) signal line and 4) time at 10-sec intervals.

At the signal 20 mg of apo-β-erythroidine was injected into the external jugular vein.

(*9*), myanesin (*2*), and glyketal (*1*). It differed from these agents in producing paralysis of much longer duration. The mean duration of paralysis with doses of 180 mg per kg was 6 min for myanesin and 35 min for apo-β-erythroidine. After 250 mg per kg of apo-β-erythroidine paralysis lasted for several hours. Death after toxic doses of apo-β-erythroidine was due to respiratory arrest. In mice the mean lethal dose was more than twice as large as the mean paralyzing dose.

Analysis of the pharmacodynamic effects of apo-β-erythroidine in cats showed that the compound did not block transmission at the myoneural junction. It produced paralysis by a depressant effect on the central nervous system. Two neuronal spinal reflexes such as the knee jerk were not affected but multineuronal reflexes such as the flexor reflex were selectively depressed by small doses of the drug. This effect together with the lack of curare-like action of the compound is illustrated in Fig. 1.

The results indicate that apo-β-erythroidine has a selective depressant action on the interneurons. It resembles in this respect other interneuronal blocking agents (*1, 2, 9*). The fact that four chemically different substances produce similar central effects and act at the same site is of great interest. They are likely to act by blocking some important but as yet unknown mechanism of transmission in the central nervous system. None of these substances interferes with the action of acetylcholine as a transmitter of nervous impulses.

It has been suspected for some time that β-erythroidine, apart from its curare-like action, also possessed central depressant properties (*3, 10*). These two properties have been dissociated in apo-β-erythroidine, which lacks the peripheral action but still retains the central depressant properties of β-erythroidine.

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Surface Action in 2,4-D Sprays[1]

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A number of workers (*1–4*) have reported increased toxicity when various substances are added to sprays of 2,4-dichlorophenoxyacetic acid used as an herbicide. Preliminary results in the summer of 1947, extensively corroborated since, show that the toxicity of these sprays may be increased several fold by adding various surface-acting substances, and suggest that some previously reported results may have been due to similar effects.

Commercial soapless powders with a base of sodium lauryl sulfate have been used most extensively as sur-

TABLE 1

YIELDS OF FLAX SEED WHEN SPRAYED WITH 2,4-D, WITH OR WITHOUT A WETTING AGENT

Spray	Surface tension of spray		Yields in bu/acre*	
	2,4-D only	Plus ½% "D"	2,4-D only	Plus ½% "D"
Water	72 dynes	28 dynes	16.4	17.4
Na salt—½ lb	58	28	13.6	*5.4*
—¼ lb	57	28	18.5	*12.2*
—⅛ lb	57	28	16.2	14.6
Amine —½ lb	53	29	15.4	*6.1*
—¼ lb	51	29	15.2	*10.7*
—⅛ lb	52	29	15.7	12.8
Ester —½ lb	34.1	30	11.7	11.2
—¼ lb	35.0	30	13.5	...
—⅛ lb	35.7	30	16.4	15.1

* Least significant difference (5%), 3.29 bu/acre.

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