[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MIAMI UNIVERSITY]

Some Alkamine Esters of Cinnamic Acid and Derivatives: Novocaine Analogs. V

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Apothesin[2] is a well-known local anesthetic. It is the γ-diethylaminopropyl ester of cinnamic acid. The configuration of apothesin is considered to be favorable to the production of anesthetic properties since the carboxyl group is connected to a carbon of an unsaturated character and the hydrogen of the carboxyl has been substituted by a propylene chain.[3]

A comparison of apothesin with β-diethylaminoethylcinnamate (an ethylene chain instead of a propylene); with β-diethylaminoethylhydrocinnamate (the carboxyl group attached to a saturated carbon instead of an unsaturated) with β-diethylaminoethylphenylpropiolate (an acid with an acetylenic instead of an ethylenic linkage); and with γ-diethylaminopropyl-α,β-dibromohydrocinnamate was undertaken to learn the influence of such modifications in the structure of apothesin on the narcotic effects of the resulting compounds on goldfish.

The belief that the linkage of the carboxyl carbon to an unsaturated carbon is essential for noticeable narcotic properties in a compound is quite generally held. On the other hand, Brill and Bulow,[4] and Cano and Ranedo[5] have investigated the anesthetic powers of certain esters of the saturated aliphatic acids and found these to possess considerable activity. Kuwahata, Ochiai and Nukita[6] in their study of the anesthetic activity on the skin of a guinea pig of several compounds which include one or more of this type, list them in the following order: phenacecaine (β-diethylaminoethylphenylacetate), hydroapocaine (β-diethylaminoethylhydrocinnamate), anisocaine (β-diethylaminoethylanisate), etc. Apparently they found the hydrocinnamate to possess anesthetic power, otherwise it could hardly be placed intermediate to two others in anesthetic power.

Gilman, Heckert and McCracken[7] report β-diethylaminoethyl acetate to be inactive while the trichloroacetate has considerable activity. The authors have included the dibromohydrocinnamate to learn if the introduction of bromine would enhance the anesthetic power of the cinnamate or otherwise. β-Diethylaminoethylphenylpropiolate is reported without

(1) A portion of a thesis offered by Clifford F. Cook in partial fulfilment of the requirements for the master's degree at Miami University.

(2) Wildman and Thorp, U. S. Patent 1,193,649.

(3) The authors acknowledge the generosity of Parke, Davis and Company in their gift of a sample of apothesin.

(4) Brill and Bulow, THIS JOURNAL, **55**, 2059 (1933).

(5) Cano and Ranedo, *Anales soc. españ. fis. quim.*, **18**, 184 (1920); *Chem. Abstracts*, **15**, 2672 (1921).

(6) Kuwahata, Ochiai and Nukita, *Folia Pharmacol. Japon.*, **7**, 408 (1928); *Chem. Abstracts*, **23**, 5236 (1929).

(7) Gilman, Heckert and McCracken, THIS JOURNAL, **50**, 437 (1928).

anesthetic power by Gilman and Pickens,[8] and this observation has been confirmed by us.

Experimental

The dibromohydrocinnamate was prepared by allowing apothesin to react with bromine in cold chloroform away from the sunlight until the theoretical amount had added on. The solubility of the derivative differed from that of apothesin in no marked respect except that it was somewhat less.

The β-diethylaminoethyl esters of (B) cinnamic acid of (C) hydrocinnamic acid and of (D) phenylpropiolic acid were prepared in the regular manner by treatment of dry benzene solutions of β-diethylaminoethanol with a slight excess of the theoretical amounts of the acid chlorides.

Phenylpropiolic acid was prepared from dibromohydrocinnamic acid by the method of Perkin[9] except using the free acid instead of the ester; yield 70%.

TABLE I

SOME PROPERTIES OF CERTAIN ALKAMINE ESTERS

	Hydrochloride		M. p., °C.	Nitrogen, % Calcd.	Found	P_H 0.008 *M* soln.
A	γ-Diethylaminopropylcinnamate	$C_{16}H_{23}NO_2 \cdot HCl$	137	..	..	6.0
B	β-Diethylethylcinnamate	$C_{15}H_{21}NO_2 \cdot HCl$	135	4.96	4.99	5.7
C	β-Diethylethylhydrocinnamate	$C_{15}H_{23}NO_2 \cdot HCl$	111	4.93	4.85	7.6
D	β-Diethylethylphenylpropiolate	$C_{15}H_{19}NO_2 \cdot HCl$	163	5.00	5.10	5.3
E	γ-Diethylpropyl-α,β-dibromohydrocinnamate	$C_{16}H_{23}Br_2NO_2 \cdot HCl$	148	3.08	3.18	4.6

TABLE II

NARCOTIC EFFECTS ON GOLDFISH

Test methods are described by Brill and Leffler, THIS JOURNAL, **55**, 365 (1933)

Hydrochloride	Concn. soln. *M*	Length of time in soln., min.	Condition when removed and fate[a]
γ-Diethylaminopropyl-cinnamate (apothesin)	0.008	20	Recovered
	.005	33	Recovered
	.003	42	Recovered
	.001	57	Recovered
β-Diethylaminoethyl-cinnamate	.008	82	Recovered
	.005	113	Recovered
	.003	131	Recovered
	.001	150	Not affected
β-Diethylaminoethyl-hydrocinnamate	.008	26	One of 3 died later, other 2 recovered
	.005	76	Sluggish only
	.003	155	Sluggish only
	.001	197	Sluggish only
β-Diethylaminoethyl-phenylpropiolate	.005	167	Died without recovery
	.003	47	Two of 3 died later
	.001	127	Unaffected
γ-Diethylaminopropyl-α,β-dibromohydro-cinnamate	.005	10	Died without recovery
	.001	42	Died without recovery

[a] Unless otherwise stated the goldfish were anesthetized when removed from the solution.

(8) Gilman and Pickens, *ibid.*, **47**, 245 (1925).

(9) Perkin, *J. Chem. Soc.*, **45**, 172 (1884).

The increase in the length of the carbon chain of the alcohol, *e. g.*, γ-diethylaminopropylcinnamate and β-diethylaminoethylcinnamate, results in quite an enhancement of the narcotic effect on goldfish. The hydrocinnamate is inactive in marked contrast to the cinnamate. In this case the saturation of the carbon chain of cinnamic acid causes a decrease in the anesthetic power of the ester. However, phenylpropiolate with the acetylenic linkage appears to be without narcotic effect on goldfish and to be quite toxic. Thus unsaturation alone is not the determinant of anesthetic power even when other groupings are favorable. The dibromohydrocinnamate is still more toxic so that goldfish were killed in a solution of as low as 0.001 molar concentration.

Summary

The properties and narcotic effects on goldfish of the esters, γ-diethylaminopropylcinnamate and α,β-dibromohydrocinnamate, and of the esters, β-diethylaminoethylcinnamate, hydrocinnamate and phenylpropiolate were studied.

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Some Nitrocyclohexylphenols and their Derivatives[1]

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Cyclohexylphenols have been prepared by a number of investigators who have used condensing agents such as fused zinc chloride, concentrated sulfuric acid and phosphorus pentoxide. Due to the ease of dehydration of cyclohexanol and the tendency for cyclohexene to polymerize, it has been found necessary to start the reaction at low temperatures. If the formation of an intermediate ether is not an essential part of the reaction mechanism, according to the views of Meyer and Bernhauer[3] we should expect the formation of cyclohexylanisole and cyclohexylphenetole as a result of the condensation of anisole or phenetole with cyclohexanol. An attempted condensation carried out under the same conditions as used for the preparation of the cyclohexylphenols failed to yield the expected products.

Since the cyclohexylphenols were observed to be rather susceptible to the oxidizing action of nitric acid this work was carried out in order to develop methods for control of their nitration. Following the method of Kartashev[4] for the nitration of phenol, in which he used ethyl acetate as a

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(3) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721–752 (1929).

(4) Kartashev, *J. Russ. Phys.-Chem. Soc.*, **59**, 819, 833 (1927); **69**, 385, 2129 (1930).