[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF MIAMI UNIVERSITY]

Alkamine Esters of Aliphatic Acids: Novocaine Analogs. IV[1]

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In the further study of the narcotic properties of alkamine esters of various acids[2] the results of an investigation of the properties of the esters of β-diethylaminoethyl alcohol and various aliphatic acids are herewith presented.

Cano and Ranedo[3] report that the various esters of dimethylamino-dimethylethylcarbinol with aliphatic acids (a) possess anesthetic powers that appear within certain limits to increase with rise of the molecular weight of the acid. (b) The esters of such dissimilar acids as benzoic, heptoic and cyclohexane carboxylic show almost equal anesthetic powers, measured by their effects on the sciatic nerve of the frog. They conclude that the approximate molecular weights of these acids account for their similarity of activity and that differences in structure may be ignored. (c) Anesthetic power increases from the butyric ester to the undecoic.

These conclusions are at variance with the statement of Gilman, Heckert and McCracken[4] "that the diethylaminoethyl esters of carboxylic acids [where the carboxyl group is attached to an unsaturated carbon atom, $RCH{=}CHCOOCH_2CH_2N(C_2H_5)_2$] show a distinct, although small, local anesthetic action. Where the same grouping is attached to a saturated carbon atom there is no local anesthetic action." Whether this generalization is meant to include the influence of the aliphatic acids is not clear. The acetate of β-diethylaminoethanol is reported by them[5] to be inactive. It is identical with the butyrate in this respect. However, a literature citation[5] by them refers to a correlation of the aromatic properties of several substances, so that they may have in mind only those acids containing the benzene ring. Their observations for the latter type undoubtedly hold true. Several esters of phenylacetic and phenylpropionic[2b] acids are known that possess no local anesthetic powers, while the corresponding esters of cinnamic acid an unsaturated acid, for example, display marked anesthetic powers.

Experimental

Narcotic properties were tested on goldfish and the P_H values determined by means of the Hellige Comparator in the manner already described.[2]

The esters were prepared by the reaction of dry benzene solutions of the theoretical amount of β-diethylaminoethyl alcohol with a slight excess over the equivalent quantity

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(2) Brill, THIS JOURNAL, **47**, 1134 (1925); **54**, 2484 (1932); Brill and Leffler, **55**, 365 (1933).

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

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

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

TABLE I

PROPERTIES OF THE HYDROCHLORIDES OF THE ESTERS OF β-DIETHYLAMINOETHYL ALCOHOL WITH ALIPHATIC ACIDS AND THE NARCOTIC EFFECTS ON GOLDFISH

Hydrochlorides, β-diethylaminoethyl	Formula	M. p., °C.	Analysis, % Cl Calcd.	Found	PH 0.008 M soln.	Mol. concn. used	Time in soln. min.	Observed effects[a]
Butyrate	$C_{10}H_{21}NO_2 \cdot HCl$	115	15.85	15.70	3.3	0.008	28.5	Never completely anesthetized
Valerate	$C_{11}H_{23}NO_2 \cdot HCl$	118	14.92	14.85	3.6	.008	6	Recovered in 11 min.
						.004	19.5	Recovered in 10 min.
						.002	54	Died without recovery
						.001	150	Not completely anesthetized
Isovalerate	$C_{11}H_{23}NO_2 \cdot HCl$	92	14.92	14.90	4.4	.008	120	Not completely anesthetized
Caproate	$C_{12}H_{25}NO_2 \cdot HCl$	127	14.21	14.25	3.7	.004	4.5	Recovered in 15 min.
						.002	4	Recovered in 17.5 min.
						.001	5	Recovered in 15 min.
						.0005	13	Recovered in 15 min.
Heptoate	$C_{13}H_{27}NO_2 \cdot HCl$	123	13.35	13.28	3.2	.004	2	Recovered in 10 min.
						.002	5.5	Recovered in 10.5 min.
						.001	18.5	Recovered in 11.5 min.
						.0005	60	Never completely anesthetized
			% N					
Pelargonate	$C_{15}H_{31}NO_2 \cdot HCl$	131	4.77	4.49	3.9	.008	4.3	Died without recovery
						.002	6.6	Recovered in 20 min.
						.0005	11.5	Recovered in 15 min.
Laurate	$C_{18}H_{37}NO_2 \cdot HCl$	107	4.17	3.99	5.2	.008	9.5	Died without recovery
						.004	13.6	Died without recovery
						.002	15	Died without recovery
						.0005	23.5	Died without recovery
Myristate	$C_{20}H_{41}NO_2 \cdot HCl$	110	3.84	3.68	5.1	.008	12	Died without recovery
						.004	19.5	Died without recovery
						.0005	36	Died without recovery
Palmitate	$C_{22}H_{45}NO_2 \cdot HCl$	111	3.57	3.58	5.8	.008	4.25	Died without recovery
						.004	12	Died without recovery
						.002	20.5	Died without recovery
						.0005	25.5	Died without recovery
Stearate	$C_{24}H_{49}NO_2 \cdot HCl$	133	3.33	3.27	6.5	.008	60	Not completely anesthetized

(For a description of methods of testing the anesthetic powers of these compounds, see Brill and Leffler, Ref. 2.)

[a] Unless otherwise stated, anesthetization of the goldfish had taken place when it was removed from the solution.

These esters have approximately the same solubilities as have the corresponding esters of the aromatic acids.[2] They show a tendency to produce soap-like solutions with water.

of the acid chloride. The reaction was completed by warming on a steam-bath under a reflux condenser for approximately an hour. White crystalline salts usually precipitated during the heating or quite soon after cooling took place. However, the hydrochloride salts of the esters of the aliphatic acids are less readily precipitated in a crystalline condition than are the corresponding salts of aromatic acids and recrystallization was necessary in some cases before well-formed crystals could be obtained.

Discussion

The butyrate is practically without anesthetic effect on goldfish but the narcotic effect increases until pelargonic acid is reached, when the toxicity is enhanced to the extent that recovery does not take place when the fish are removed from the anesthetizing solution. The isovalerate is less active than the normal valerate.

These results on goldfish are in close harmony with those announced by Cano and Ranedo[3] on frogs. They found the maximum activity for the ester of undecylic acid and contradict the assumption of the absolute need of unsaturation in the acid making up a part of the local anesthetic.

The P_H's of these esters are in general lower than those of aromatic acids. Undoubtedly local anesthetics must possess low acidity, otherwise irritability results and any local anesthetic property that may be present is counteracted or concealed.

Summary

The hydrochlorides of the esters of β-diethylaminoethyl alcohol with butyric, *n*-valeric, isovaleric, caproic, heptoic, pelargonic, lauric, myristic, palmitic and stearic acids have been made, and their narcotic effects on goldfish and their P_H values determined.

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