

# AN EXAMINATION OF THE LOCAL ANESTHETIC ACTION OF SOME SYNTHETIC SWEET SUBSTANCES AND OTHER PHENYL ALKYL DERIVATIVES \* †

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THE anesthesiologist has at his disposal a variety of local anesthetic agents none of which, however, approximates the ideal. It is for this reason that the search continues for new anesthetics with lower toxicities, longer durations of action, and wider ranges of applicability. Several years ago Verkade § and associates (1), in describing the preparation of some synthetic sweet substances, found that all of the sweet compounds synthesized by them possessed local anesthetic activity. It seemed to us that such substances deserved further investigation for possible application to clinical anesthesiology.

Originally Blanksma and van der Weyden (2) demonstrated that 4-nitro-2-aminophenyl alkyl ethers (formula 1, fig. 1) have an intensely sweet taste while 2-nitro-4-aminophenyl alkyl ethers (formula 2, fig. 1) are tasteless. According to Verkade et al. (1) all of the sweet compounds possessed more or less local anesthetic activity. Formula 3, figure 1, was said to be about thirty times as potent as cocaine. We had prepared for us || salts of several similar compounds the structural formulas of which are shown in figure 2 along with a brief listing of their physical characteristics. Because these substances possess some undesirable characteristics, our investigations have not been extensive. We are presenting our results in the hope that further studies may yield other valuable agents for clinical anesthesiology.

## METHOD OF STUDY

Solutions of the substances studied were instilled into the conjunctival sacs of rabbits and compared for anesthetic activity with cocaine. In a few instances other familiar anesthetic agents were employed for comparison. The solutions were held in contact with the cornea usually for one minute, the conjunctival sac then rinsed

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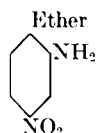
§ Because of wartime restrictions on the circulation of publications we have been unable to secure Verkade's description of the synthesis of the substances in figure 1.

|| Charles A. Dunning, M.D., synthesized these compounds.

with saline solution, and the onset and duration of corneal anesthesia noted. Stimulation of the cornea was accomplished by a modification of Regnier's (3) multiple stimulation technic employing a blunt tipped pencil as recommended by Sollmann (4). During and after the procedure an effort was made to discern evidences of irritation on the cornea and conjunctiva.

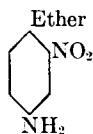
FIGURE 1

## I. Sweet Substance (Anesthetic)



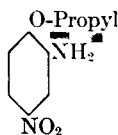
4-Nitro-2-Aminophenyl Alkyl Ether

## II. Tasteless Substance (Not Anesthetic)



2-Nitro-4-Aminophenyl Alkyl Ether

## III. "Substance 30 X Potency of Cocaine"



1-Propoxy-2-Amino-4-Nitrobenzene

The lethal toxicity of one of the substances was determined by injecting it into the peritoneal cavity of young albino rats and observing the behavior of the animals until death or recovery ensued. The organs of the animals which succumbed were examined microscopically.

## RESULTS OF EXPERIMENTS

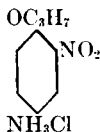
## A. Corneal Anesthesia:

The results of instillations in the conjunctival sac of rabbits are presented in table 1. It will be seen that anesthesia, if present at all, was usually attained in one half to two and a half minutes after application. Most of the solutions including cocaine were variable in action, sometimes producing anesthesia and at other times failing to do so. This inconstancy of action, however, was more pronounced with the

phenyl alkyl derivatives prepared for us than with the standard anesthetic agents. Some solutions, procaine included, never produced anesthesia; others resulted in anesthesia more lasting than cocaine but with greater inconstancy. Polyethylene glycol 400, a solvent for one of the compounds, produced no anesthesia. Nupercaine, on the other hand, resulted in the most prolonged anesthesia and was effective

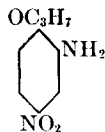
FIGURE 2

No. 232



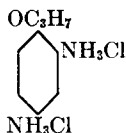
Amine Hydrochloride 2%  
Soluble in H<sub>2</sub>O  
pH 2-3?  
Taste—Salty and Bitter  
Color—Amber

Nopa



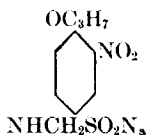
Not H<sub>2</sub>O Soluble  
Soluble 2% in Polyethylene Glycol 400  
Said to be 6 times potency of cocaine  
(Chem. Zentr. II: 2897, 1942)

No. 238



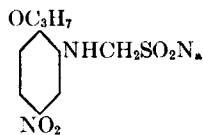
Crude sample—Difficult to purify  
pH 6-6.5

No. 232 SFX



Water Soluble  
Sodium Formaldehyde  
Sulfoxalate Compound  
Bitter Taste  
pH about 7.5

Nopa SFX



Water Soluble  
Sodium Formaldehyde  
Sulfoxalate Compound  
Sweet Taste  
pH about 7.5

in greatest dilution. None of the solutions appeared to be markedly irritating, although No. 232 caused the greatest discomfort to the animals. Some of the solutions ineffective in weak concentrations eventually were proved to be anesthetic in action by repeated rapid instillation.

### B. Toxicity:

The toxicity of No. 232 (1 per cent aqueous) was determined by intraperitoneal injection in rats weighing from 90 to 180 Gm. The median lethal dose appeared to be about 300 mg. per kilogram of body weight. Characteristic behavior patterns were observed in most animals regard-

less of the final outcome. Within one to two minutes after injection ataxia appeared, followed rapidly by unconsciousness, rapid shallow respirations, and clonic movements of the extremities or extension of the limbs on one side or the other. The animals might remain in this state for five to twenty-four hours. If recovery was to be the outcome, they regained equilibrium within a few hours; their fur was ruffled and wet. Some of the dead animals were found with their heads submerged in the drinking troughs. These phenomena do not resemble those described as resulting from "speed shock" (5). Microscopic examination

TABLE 1  
DETERMINATION OF CORNEAL ANESTHESIA

Substance Per Cent in Aqueous Solution	Number of Tests	Minutes Applied	Onset of Anesthesia (Minutes)	Duration of Anesthesia (Minutes)	
				Range	Average
232—1%	17	0.5	1.5—2.5	0—20.5	8.4
232—1%	3	1.0	1.5	16—21	19.1
232—0.1%	5	1.0	0	0	0
232—0.5%	10	1.0	0—2	0—17	3.9†
232SFX—1%	6	1—2	0	0	0
238—1%	10	1	2	0—16	4.8
Nopa-SFX—1%	6	1—2	0	0	0
Nopa—1%*	16	1.0	2	1—23	11.7
Cocaine—1%	6	0.5	2	9—13	10.9
Cocaine—1%	4	1.0	1.5—2.5	0—15	9.6
Cocaine—0.1%	5	1.0	4—6	0—8	3.2†
Cocaine—0.5%	2	1.0	2	6—8	14.0
Polyethylene Glycol 400—100%	2	1.0	0	0	0
Procaine—1%	3	1.0	0	0	0
Nupercaine 1:1500	1	1.0	1		60

\* 1 per cent in polyethylene glycol 400.

† Repeated instillation.

of the organs of one animal found dead two days after injection revealed moderate congestion in the liver with granularity of the liver cells and mild vacuolization of the cells about the central vein. The kidney in this animal exhibited swollen granular cells lining the convoluted tubules, with acidophilic material in the lumens of the tubules. Another animal dead in one day was found to have diffusely scattered areas of acute necrosis in the liver and spleen; in the kidney, the glomeruli were swollen and congested, with granular debris in the glomerular spaces, and the collecting tubules were lined by vacuolated disintegrating cells. It is likely that too short a period had intervened between injection and death to have resulted in more specific pathologic changes.

## DISCUSSION OF RESULTS

Of the compounds synthesized, only solution No. 232 effected corneal anesthesia. The anesthesia lasted longer but was more variable in action than cocaine. All of the substances, the formulas of which appear in figure 2, present certain unsatisfactory characteristics as anesthetic agents in so far as solubility, pH, and color are concerned. The MLD/50 of compound No. 232 is not high when compared with anesthetics in clinical use (6), but the mode of death resulting from its injection is entirely different from that observed with ordinary anesthetics. Beutner and Calesnick (7) tested 18 anesthetic agents on the rabbit cornea and determined the convulsive doses for guinea pigs. They found that all effective local anesthetics had a similar typical chemical structure and were convulsive agents in doses equal to one-half to one-quarter of the lethal dose. The effective anesthetics were ester-like combinations of an amino acid with p-amino benzoic acid or with another benzoic acid derivative. Beutner and Calesnick drew the conclusion that no compound without an ester structure can be an efficient nonirritating local anesthetic. Their conclusions seem to be justified in so far as the results of our few experiments with the particular compounds studied are concerned.

## SUMMARY

The anesthetic activity of several phenyl alkyl derivatives was observed on the rabbit cornea and compared with that of cocaine. None of these compounds proved to be as efficient as cocaine and, in addition, presented other undesirable characteristics which might preclude their use for clinical purposes.

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