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Local Anesthetic Activity of a Series of Phenyl Piperidine Derivatives.*

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A number of piperidine derivatives (Table I) have been made available† to us for pharmacological study. The structure of these compounds suggested the present experiments which were designed to determine if they exhibited local anesthetic properties. Comparisons of their activity were made with the diethylaminoethyl ester of aminobenzoic acid (procaine) and with methyl benzoyl ecgonine (cocaine).

Dermal Anesthesia. The technic described by Rose[1] has been employed to detect the presence or absence of anesthesia after intradermal injection of the piperidine compounds in guinea-pigs. The standard of comparison for duration of anesthesia was procaine. In the present experiments, 1.0% solution of procaine produced anesthesia for an average period of 28 minutes, and the piperidine compounds for average periods of from 41 to 75 minutes (Table I). While the anesthesia produced by the piperidine derivatives was more prolonged than that obtained after procaine, all of the new derivatives caused hyperemia, followed in most cases by necrosis at the site of injection.

Corneal Anesthesia. The presence or absence of corneal anesthesia was tested in rabbits using the method previously described.[2] One per cent solution of cocaine hydrochloride, which served as the standard of comparison for duration of topical action, produced anesthesia for an average of 21 minutes (Table I). One per cent solutions of III, IV, V, VII, VIII and IX produced anesthesia for periods of from 21 to 90 minutes (Table I). All of these caused irritation as evidenced by capillary engorgement, except III, which in 1.0% solution did not cause pitting or appear irritating. Compounds VI, X, XI and XII in 1.0% solution failed to induce anesthesia of rabbit cornea by topical application.

Toxicity. In mice by intraperitoneal injection the MLD of compounds III, IV, XI and XII appeared to be in the neighborhood of 100 mg/kg (Table I). The MLD of VIII and IX is approximately 150 mg/kg of body weight and that of V above 100 (Table I). In these experiments the MLD of cocaine hydrochloride was found to be between 100 and 150 mg/kg of body weight (Table I).

Summary. A number of new phenylpiperidine derivatives (α-4-methyl-(III), β-4-methyl-(IV), 4-dimethyl-(V), 4-methylol-(VI), α-4-phenyl-(VII), β-4-phenyl-(VIII), α-4-carboxylic acid-(X), α-4-carbomethoxy-(XI), α-4-carbethoxy-(XII), 3-phenyl-piperidine) were found to produce anesthesia after intradermal injection in guinea-pigs which was more prolonged than that observed after procaine. All of the new compounds induced hyperemia followed in most cases by necrosis at the site of injection. After topical application 1.0% solutions of III, IV, V, VII or VIII produced corneal anesthesia in rabbits. In 1.0% solutions VI, X, XI or XII failed to exhibit topical activity in rabbits. Intraperitoneally in mice the acute toxicity of the new derivatives was in the range of that of cocaine.

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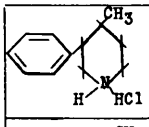
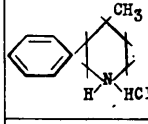
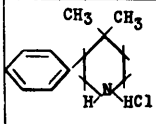
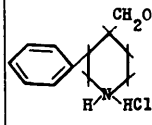
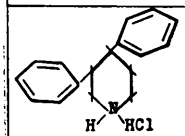
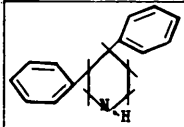
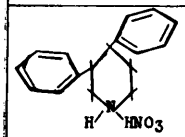
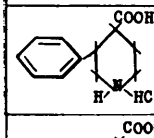
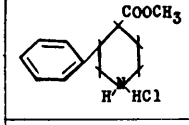
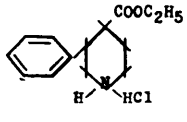
† These compounds were prepared and made available to us by Dr. Frederick Koelsch of the Department of Organic Chemistry, University of Minnesota.

1 Rose, C. L., *J. Lab. Clin. Med.*, 1929, **15**, 128.

2 Fellows, E. J., PROC. SOC. EXP. BIOL. AND MED., 1943. **53**, 7.

TABLE I.
Duration of Local Anesthesia and Toxicity.

Formula	Code No.	M.P. °C	Duration of anesthesia: Guinea pig skin 1% min.	Duration of anesthesia: Rabbit cornea 1% min.	Toxicity Mice—Intraperitoneally No. died/No. used mg per kg: 100	Toxicity Mice—Intraperitoneally No. died/No. used mg per kg: 150
	Cocaine			21	5/10	10/10
	Procaine		28			
 (α)	III	170-175	58	26	7/8	
 (β)	IV	248-252	58	21	8/8	
	V	274-276	49	34	5/8	
 (α)	VI	105-111*	41	No anesthesia	Not tested	
 (α)	VII	194-198	75	50	4/11	
 (β)	VIII	115-116	69	40	3/20	8/8
 (β)	IX	160-162 H_2O off at 140	63	90	2/20	8/8
 (α)	X	>275	49	No anesthesia	Not tested	
 (α)	XI	253-255	73	" "	7/8	
 (α)	XII	245-246	56	" "	6/6	

* B.P. 215-218°.