(PCAM) and hydroxylamine. An equilibrium constant, $k_{eq.}$, can be determined at any pH value. The equilibrium constant for reaction 2 is

$$k_{eq.} = \frac{(PCAM)(NH_2OH)}{(2\text{-}PAM)} \qquad \text{(Eq. 15)}$$

The basic dissociation constant for hydroxylamine may be arranged as

$$\frac{(NH_2OH)}{(NH_3OH)^+} = \frac{(OH^-)}{Kb} = \frac{Kw}{Kb\,(H^+)} \qquad \text{(Eq. 16)}$$

Substituting Eq. 16 into Eq. 15 and since the concentration of $(NH_3OH)^+$ is equal to the concentration (PCAM)

$$k_{eq.} = \frac{Kw\,(PCAM)^2}{Kb(H^+)\,(2\text{-}PAM)} \qquad \text{(Eq. 17)}$$

The value of $k_{eq.}$ for the reactions in our study at 87° was approximately 20.

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Synthesis of Some N-Aralkyl-N-methylaminoethyl Carbanilates

By ROGER W. BARNES and WILLIAM J. ROST

In an attempt to correlate the basicity of local anesthetics with their activity, 21 substituted carbanilates of N-benzyl-N-methylaminoethanol, N-phenethyl-N-methylaminoethanol, and N-phenpropyl-N-methylaminoethanol were prepared. Substitutions on the carbanilic acid portion of the molecule were designed to study possible resonance effects. The compounds showed topical local anesthetic properties, but infiltration anesthetic properties were almost absent. No correlation between basicity and local anesthetic properties could be made. The relatively high acidity of the hydrochloride salts tested might account for the irritation commonly found.

CARBANILIC ACID esters of aminoalcohols have been reported to have marked local anesthetic activity (1, 2). Carbanilates with alkyl, chloro, amino, and alkoxy substitutions have been shown to possess a fair to high degree of local anesthetic activity (3–11). The position of the substitutions on the phenyl group have favorably affected the activity of the compounds in some cases (4, 6, 9). Sekera and Vrba have concluded that the more stable carbamates had a greater activity (6).

Aralkyl substitution on the nitrogen of aminoalkyl esters has given compounds with marked local anesthetic action. A 2% solution of γ-(2-benzylpiperidino)propyl benzoate or γ-(2-phenethylpiperidino)propyl benzoate gave a corneal anesthesia lasting 5 to 6 days (12). β-(N-Methyl-N-phenethylamino)ethyl carbanilate administered intracutaneously to a guinea pig in 0.5% concentration, gave an anesthetic effect lasting more than 24 hours. The local anesthetic effect of this compound lasted 84 minutes when used on the rabbit cornea (13).

Because the aromatic substitutions gave a marked increase in the activity of dialkylaminoalkyl carbanilates and because N-aralkylation of the aminoalkyl benzoates, *p*-aminobenzoates, and the carbanilate proved effective, it was thought to be of interest to investigate the N-aralkylation of aminoalkyl esters of substituted carbanilic acids. Tolstoouhov has postulated that the local anesthetic effect of a molecule is related to the basicity of the amine nitrogen it contains (14). The N-aralkyl groups chosen for investigation were benzyl, phenethyl, and phenpropyl. The N substitutions might then vary the basic charac-

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ter of the amine and therefore vary the activity of the compounds as local anesthetics. Carbanilates, methylcarbanilates, chlorocarbanilates, methoxycarbanilates, and nitrocarbanilates of the N-phenalkyl-N-methylaminoethanols were prepared. The nitrocarbanilates could then be reduced to the amino derivatives after the initial reaction. These substituted carbanilates were chosen to vary the resonance effects of the carbamic acid esters. *Meta-* and *para-*substitutions were chosen to contrast the different resonance effects. *Ortho-* substituted carbanilates were not studied because of the possible steric hindrance.

The purpose of this paper is to report the synthesis of 21 compounds, report their basicities, and to give a preliminary evaluation of their local anesthetic activities.

EXPERIMENTAL

N - Phenalkyl - N - methylaminoethanols.—The proper phenalkyl halide was condensed with two equivalents of N-methylaminoethanol in the absence of a solvent. The exothermic reactions were first cooled in an ice bath and then allowed to stand at room temperature for varying lengths of time. After treatment with aqueous sodium hydroxide, the reaction mixture was extracted with ether. The ether was evaporated, and the aminoalcohol was distilled under reduced pressure. The products are described in Table I.

Carbanilates.—A solution of 0.066 *M* of the appropriate isocyanate dissolved in 30 ml. of dry toluene was slowly added to 0.06 *M* of the N-phenalkyl-N-methylaminoethanol. After the initial heat of reaction had subsided, the mixture was refluxed for 3 hours and allowed to stand at room temperature for 2 days. At the end of this period, the urea which had formed was filtered from the solution. Anhydrous hydrogen chloride was passed into the filtrate to obtain an oil which changed on standing to the solid hydrochloride salt. The crude product was recrystallized from acetone to which a trace of ethanol had been added.

Reduction of Nitrocarbanilates.—The nitrocarbanilates on reduction with hydrogen under low pressure with platinum oxide yielded an oil which solidified on standing. Attempts at recrystallization were unsuccessful.

The carbanilates prepared are listed in Table II.

Comparison of Basicities of Derivatives.—The basicities of the various compounds were compared using the method of Tolstoouhov (14). The pKb of each compound was also determined. A solution of the amine hydrochloride was dissolved in water. The salt was half neutralized by the addition of 0.01 *N* sodium hydroxide. Because of the insolubility of the free base, alcohol was added to facilitate solution. The pH of the resultant solution was determined, and the pKb calculated. The results of the above determinations are reported in Table III.

TABLE I.—AMINOALCOHOLS

Compound	B.p., °C.	% Yield
$C_6H_5—CH_2—N(CH_3)—CH_2CH_2OH$	124–129/8 mm. Hg	83
$C_6H_5—(CH_2)_2—N(CH_3)—CH_2CH_2OH$	143–145/10 mm. Hg	51
$C_6H_5—(CH_2)_3—N(CH_3)—CH_2CH_2OH$	173–178/20 mm. Hg	66

TABLE II.—N-PHENALKYL-N-METHYLAMINOETHYL CARBANILATES
$R—C_6H_4—HN—CO—O—CH_2CH_2N(CH_3)R'$

R	R'	M.P., °C.	Yield, %	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	$C_6H_5CH_2$—	167–168	58.2	63.64	63.28	6.60	6.23
m CH_3—	$C_6H_5CH_2$—	167–168	55.7	64.56	63.86	6.92	6.33
p CH_3—	$C_6H_5CH_2$—	210–212	56.9	64.56	64.58	6.92	6.36
m Cl—	$C_6H_5CH_2$—	165–166	72.7	57.47	56.50	5.67	5.34
p Cl—	$C_6H_5CH_2$—	209–211	60.0	57.47	57.67	5.67	5.59
p CH_3O—	$C_6H_5CH_2$—	169–170	42.7	61.62	61.72	6.61	6.73
m O_2N—	$C_6H_5CH_2$—	118–120	36.4	...	...	...	...
p O_2N—	$C_6H_5CH_2$—	212–214	42.7	...	...	...	...
H	$C_6H_5(CH_2)_2$—	186–188	69.0	64.56	64.67	6.92	6.56
p CH_3—	$C_6H_5(CH_2)_2$—	208–210	77.5	65.41	65.53	7.22	7.05
p Cl—	$C_6H_5(CH_2)_2$—	210–212	95.0	58.54	58.94	6.01	5.84
p CH_3O—	$C_6H_5(CH_2)_2$—	192–193	82.5	62.54	62.47	6.91	6.67
p O_2N—	$C_6H_5(CH_2)_2$—	97	78.7	62.96	62.62	6.17	6.28
H	$C_6H_5(CH_2)_3$—	165–166	65.4	65.41	65.30	7.22	7.00
m CH_3—	$C_6H_5(CH_2)_3$—	139–140	59.1	66.19	65.26	7.50	7.28
p CH_3—	$C_6H_5(CH_2)_3$—	165–166	78.3	66.19	66.37	7.50	6.93
m Cl—	$C_6H_5(CH_2)_3$—	185–186	69.4	59.53	58.85	6.31	6.72
p Cl—	$C_6H_5(CH_2)_3$—	165–166	51.1	59.53	59.49	6.31	6.38
p CH_3O—	$C_6H_5(CH_2)_3$—	135–137	58.1	63.40	63.64	6.92	6.99
m O_2N—	$C_6H_5(CH_2)_3$—	161–162	39.6	...	...	...	...
p O_2N—	$C_6H_5(CH_2)_3$—	165–167	58.8	...	...	...	...

TABLE III.—BASICITY OF CARBANILATES

Substitution	pH at Which Solution Becomes Cloudy[a]	pKb
Substituted Carbanilates of N-Benzyl-N-methylaminoethanol		
H	6.15	7.40
m-Methyl	5.59	7.42
p-Methyl	5.59	7.47
m-Chloro	5.19	7.58
p-Methoxy	6.09	7.37
Substituted Carbanilates of N-Phenethyl-N-methylaminoethanol		
H	6.19	7.10
p-Methyl	5.77	7.02
p-Chloro	5.38	7.05
p-Methoxy	6.12	7.14
Substituted Carbanilates of N-Phenpropyl-N-methylaminoethanol		
H	5.59	6.82
m-Methyl	5.75	6.88
m-Chloro	5.15	6.92
p-Chloro	5.35	7.01
p-Methoxy	6.11	7.11

[a] Done according to method of Tolstoouhov (14).

PHARMACOLOGY

The local anesthetic activity of the compounds was determined on the mouse cornea. With two exceptions, the compounds were active in concentrations of 0.5% or less. N-Benzyl-N-methylaminoethyl *p*-methylcarbanilate and N-benzyl-N-methylaminoethyl *m*-methylcarbanilate were active in concentrations as low as 0.05%. Irritation was commonly found. Only the N-benzyl-N-methylaminoethyl carbanilate, *m*-methylcarbanilate, and *p*-methylcarbanilate showed local anesthetic activity when injected intradermally into the guinea pig back. Irritation was commonly found when this method of testing was used.

The N-benzyl-N-methylaminoethyl carbanilate, *m*-methylcarbanilate, and *p*-methylcarbanilate were tested for any possible action they might have on the rat intestine. A decrease in motility was observed with the most marked decrease being with the N-benzyl-N-methylaminoethyl *p*-methylcarbanilate.

The minimum lethal doses of these compounds was of the order of 200 mg./Kg.

DISCUSSION

Tolstoouhov has postulated that compounds whose basicity fell within a certain range would be local anesthetics (14). Local anesthetic salts which start to separate from solution as the free base at pH 5.93–6.36 were claimed to have the highest order of activity. Compounds possessing a basicity outside of this optimum range were shown to have a gradually diminishing activity. The above postulation was not found to hold in this series of carbanilates. The best local anesthetic activity was found in the N-benzyl-N-methylaminoethyl carbanilates. Although compounds in the other series possessed a basicity which fell within the optimum range suggested by Tolstoouhov, they showed no intradermal local anesthetic activity. Almost all of the compounds, however, did show a topical activity. No correlation between basicity and local anesthetic activity was possible.

The pKb of the compounds indicated that they were relatively weak bases. The acidity of the hydrochloride salts tested could then explain the irritation commonly found in this series. A similar explanation might be given for the irritant compounds reported by Sievers and McIntyre (13).

The electronic influences of the aromatic substitutions on the carbanilic acid portion of the molecules seemed to have no effect on the local anesthetic activity.

SUMMARY

The syntheses and properties of 21 N-aralkyl-N-methylaminoethyl carbanilates were described.

The compounds tested possessed a topical local anesthetic effect in concentrations of 0.5% or less. Infiltration anesthetic properties were almost absent.

The relative basicities of the compounds were determined, but no correlation with local anesthetic activity could be made. The relatively high acidity of the hydrochloride salts tested might account for the irritation commonly found.

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