A crystalline precipitate appeared in solutions of several concentrations of butacaine sulfate in 1.2 and 1.5% sodium chloride before the addition of blood. In contrast to the effect produced on butacaine sulfate solutions by increased proportions of sodium chloride, several solutions of pramoxine hydrochloride in some concentrations of sodium chloride exhibited evidence of precipitation after incubation and centrifugation of the blood-salt mixtures. Higher concentrations of sodium chloride appeared to decrease the precipitation until the effect was eliminated as far as visual observation could detect.

Experimental data indicated that phenmetrazine hydrochloride did not behave in a manner similar to any of the other compounds studied in this investigation. As the concentration of sodium chloride was increased, a corresponding augmentation in the degree of hemolysis, compared to that produced in the presence of 0.6% sodium chloride, was effected. The only exception to this trend was exhibited by 5.40% phenmetrazine hydrochloride solutions in environments of 0.6, 0.9, 1.2, and 1.5% sodium chloride; essentially complete hemolysis was elicited in the presence of 0.6% sodium chloride, and increasing the concentration of sodium chloride afforded no apparent change in the degree of hemolysis.

SUMMARY

1. An increase in the concentration of sodium chloride reduced the degree of hemolysis produced by procaine hydrochloride, 2-propoxyprocaine hydrochloride, and ammonium salicylate solutions in an environment of 0.6% sodium chloride. A similar effect was noted in most of the concentrations of ammonium benzoate studied.

2. Increasing the concentration of sodium chloride in solutions of pramoxine, benoxinate, and hexylcaine hydrochlorides, and butacaine sulfate afforded some reduction in the degree of hemolysis produced by the compound in 0.6% sodium chloride in cases where the degree of hemolysis was slight. No reduction in the degree of hemolysis was observed as a result of augmenting the sodium chloride concentration when the compound under examination caused degrees of hemolysis ranging from intermediate to essentially complete in the presence of 0.6% sodium chloride.

3. Higher concentrations of sodium chloride generally increased the degree of hemolysis produced by phenmetrazine hydrochloride solutions in the presence of 0.6% sodium chloride. In the case of 5.40% solutions of phenmetrazine hydrochloride, hemolysis was essentially complete in presence of 0.6, 0.9, 1.2, and 1.5% sodium chloride.

4. No appreciable discoloration of oxyhemoglobin resulted from the presence of 0.1% sodium carbonate. Triple distilled water, 0.1% sodium chloride, 0.1% sodium carbonate, 0.01% saponin, and a solution containing 0.1% sodium carbonate and 0.01% saponin caused the same degree of hemolysis within experimental error.

5. The slight time lapse between the addition of blood to the solution under study and the subsequent shaking of the mixture seemed to produce no appreciable variation in experimental data.

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Modification of Physical Properties of Certain Antitussive and Antihistaminic Agents by Formation of N-Cyclohexylsulfamate Salts

By JAMES A. CAMPBELL and JAMES G. SLATER

The N-cyclohexylsulfamic acid salts of four well known therapeutic agents were prepared. Salts of two of the compounds, dextromethorphan and chlorpheniramine, were found to have greatly improved taste and increased solubility. Accelerated aging studies indicate good stability.

PROMINENT among the factors which must be considered in the development of oral dosage forms are those of solubility and taste acceptability. These factors present no great problem provided the drug is to be administered in such dosage forms as capsules or tablets which are designed to be swallowed as a unit. However, in those cases where it is desirable to administer a drug in liquid form, chewable tablet, lozenge, or other such forms, solubility and taste acceptability become factors of prime consideration.

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Some drugs present no taste problem because most people do not find the characteristic taste objectionable. Many drugs, even though moderately distasteful, are acceptable to some people because they are therapeutic agents and are not intended to appeal to the gustatory sense. However, it appears that people, in general, have come to expect and demand palatability in therapeutic agents.

Unpleasant tastes are overcome or improved upon in various ways. The usual method involves the judicious selection and use of additives. Cook (1) noted three factors in successful flavoring of pharmaceuticals: "(*a*) selection of a harmonious flavor, (*b*) effective masking, and (*c*) utilizing the undesirable taste as a base upon which a palatable formulation is built." Entrekin and Becker (2) found that the following would aid in disguising the bitter taste of quinine hydrochloride; adding citric acid, adding sodium chloride to some types of syrups, increasing sugar concentration, and increasing viscosity. In a recent survey of types of flavors used by pharmaceutical manufacturers for improving taste, Wesley (3) divided the flavors into two main categories: (*a*) fruit, and (*b*) nonfruit. It was observed that there was a trend toward the use of fruit flavors with a single flavor being used in 72% of the cases and with a combination being used in 28% of the cases. Pharmaceutical flavors (4) in descending order of frequency of use were found to be cherry, fruit (nonspecific), orange, raspberry, chocolate, and mint.

With the skillful application of masking and flavoring techniques available, one can usually produce an acceptable product provided there are no stringent restrictions on dilution. However, in cases where it is desirable to administer drugs in a rather concentrated form, such as drop dosage, the usual methods of taste control are sometimes inadequate. In such a situation, one must seek other ways of dealing with the taste problem while keeping in mind the solubility limitations.

Conceivably, one might be able to modify the taste characteristics of certain drugs by formation of salts or complexes of the drug which have more acceptable taste characteristics. This might be achieved in either of two ways; the formation of an insoluble compound which would be tasteless (5), or the formation of a soluble salt possessing an improved taste. One obvious disadvantage of the former would be the insolubility which would preclude its use as a solution. On the other hand, the formation of a soluble salt with improved taste is not always easy to achieve.

The objective in the study to be described was the formation of soluble, palatable, stable salts of certain characteristically bitter amine drugs. Four well-known therapeutic agents were chosen for the study: two antitussive agents—noscapine and dextromethorphan; and two antihistaminic agents—thenylpyramine and chlorpheniramine (6). The drugs, in the form of the free bases, were caused to react with N-cyclohexylsulfamic acid to form the corresponding salts.

A preliminary taste evaluation of the resulting salts was performed as follows: Aqueous solutions of the new salts as well as the commonly occurring salts were prepared in 0.004 *M* concentration. The solutions were tasted by a panel of six people. The dextromethorphan and chlorpheniramine salts of N-cyclohexylsulfamic acid were judged to be superior to the original salts (dextromethorphan hydrobromide and chlorpheniramine maleate) by the panel, whereas the new salts of noscapine and thenylpyramine were judged to have no advantage over the original forms. The latter two compounds were not considered further but the dextromethorphan N-cyclohexylsulfamate and chlorpheniramine N-cyclohexylsulfamate were subjected to further investigation.

EXPERIMENTAL

Formation of the Salts

Two different methods for forming the salts were utilized. These will be referred to as Methods A and B.

Method A.—Equivalent quantities of N-cyclohexylsulfamic acid and the free amine base were placed in a round-bottomed flask. Absolute ethanol was added in the proportion of 4 ml. of ethanol to each Gm. of N-cyclohexylsulfamic acid. This mixture was refluxed for a period of 1 hour and then concentrated to approximately one-half its original volume. Approximately three times its volume of ether was added to cool the solution. After precipitation was complete, the precipitate was collected on a filter and dried under vacuum.

Method B.—A slurry of the free base in water was titrated with a 0.1 *N* solution of N-cyclohexylsulfamic acid to the end point using a titrimeter. There was a gradual dissolution of the base as the end point was approached with a complete disappearance at the end point. The solution was evaporated to dryness using a Rinco evaporator at temperatures ranging up to 85°.

Dextromethorphan N-Cyclohexylsulfamate

The compound is a white granular substance. One gram is soluble in 9.7 ml. water. Melting characteristics are as follows: 80° (partial liquefaction), 217–218° (decompn).

Anal.—Calcd. for $C_{18}H_{25}NO \cdot C_6H_{13}NO_3S \cdot H_2O$, M. W. 468.66: N total, 5.99. Found: N total (Kjeldahl), 6.14.

Infrared Spectra.—Infrared spectra of equivalent concentrations of dextromethorphan N-cyclohexyl-

sulfamate and of an equimolar mixture of dextromethorphan and N-cyclohexylsulfamic acid were run in potassium bromide pellets. The spectra are shown in Fig. 1. Certain absorption peaks appeared in the spectrum of the compound but were absent in the spectrum of the reactants. These peaks were found at the following points: 760, 800, 1150, and 1170 cm.$^{-1}$. On the other hand, certain absorption peaks appeared in the spectrum of the mixture but were absent in the spectrum of the compound. These were observed at the following points: 705, 820, 1050, 1220, 1231, 1250, and 3250 cm.$^{-1}$.

Optical Rotation.—The compound was found to have the following optical rotation: $[\alpha]_D^{25} = +28°$ to $+29°$ (2.5% solution in water).

Stability Studies.—Aqueous solutions of the compound were prepared at pH levels of 4, 5, 6, and 7 using phthalate–NaOH and KH_2PO_4–NaOH buffer mixtures. After assay by optical rotation, the solutions were placed in an oven at 50°. The solutions were assayed and inspected at the end of 1 month and 6 months. The results are shown in Table I. From the data it appears that dextromethorphan N-cyclohexylsulfamate in aqueous solution has good stability when maintained at a pH not greater than 4.

TABLE I.—STABILITY OF DEXTROMETHORPHAN N-CYCLOHEXYLSULFAMATE IN AQUEOUS SOLUTION AT 50°

	Original	One Month		Six Months	
pH	% Found	% Found	Appearance	% Found	Appearance
4	2.14	2.13	No change	1.83	Some sediment
5	2.11	1.22	Little sediment	...	Sediment
6	2.09	0.74	Sediment	...	Sediment
7	2.10	0.58	Sediment	...	Sediment

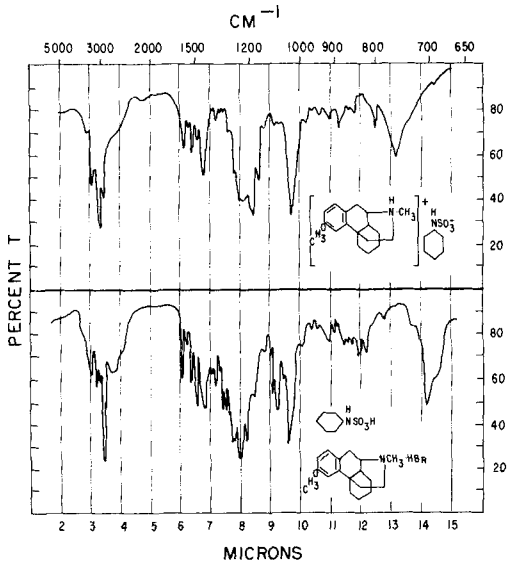

Fig. 1.—Infrared spectra of dextromethorphan N-cyclohexylsulfamate (upper section) and an equimolar mixture of dextromethorphan hydrobromide and N-cyclohexylsulfamic acid (lower section).

Chlorpheniramine N-Cyclohexylsulfamate

This compound appears as a white, or slightly pink crystalline substance. One gram is soluble in 10 Gm. of water. The melting point was found to be 90–95°. It was found to have an absorption maximum at 262 mμ.

Anal.—Calcd. for $C_{16}H_{19}ClN_2 \cdot C_6H_{13}NO_3S$, M.W. 454.04: N total, 9.25; Cl, 7.8. Found: N total (Kjeldahl), 9.27; Cl, 7.73.

Infrared Spectra.—Infrared spectra of equivalent concentrations of chlorpheniramine N-cyclohexylsulfamate and of an equimolar mixture of chlorpheniramine and N-cyclohexylsulfamic acid were run in potassium bromide pellets. The spectra are shown in Fig. 2. Certain absorption peaks appeared in the spectrum of the compound that were absent in the spectrum of the mixture. These peaks can be observed at 940, 1122, and 1550–1560 cm.$^{-1}$. Likewise, certain peaks were found in the spectrum of the mixture that were absent in the spectrum of the compound. These peaks can be observed at 725, 780, 830, 1200, 2700, and 3500 cm.$^{-1}$.

Stability Studies.—Aqueous solutions were prepared in a concentration of approximately 0.4%. The solutions were buffered at pH 4, 5, 6, and 7, respectively. The solutions were assayed by ultraviolet absorption at 262 mμ using a 0.4% chlorpheniramine maleate solution as the standard. After assay, the solutions were placed in an oven at 50°. The solutions were inspected and assayed at the end of 2 months. The results are shown in Table II. From the data contained in Table II it appears that chlorpheniramine N-cyclohexylsulfamate solution possesses good stability when maintained at a pH of 4.

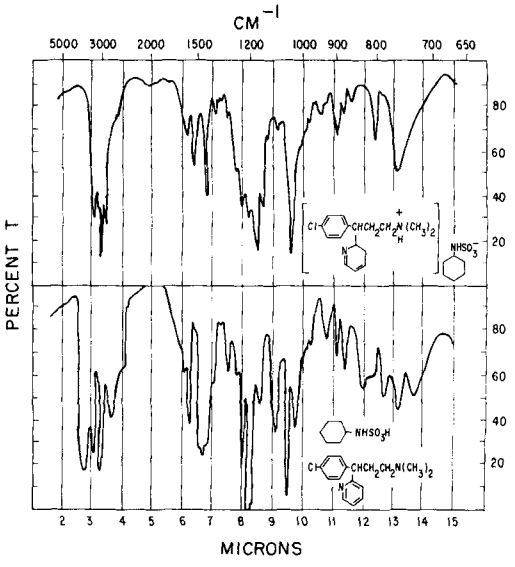

Fig. 2.—Infrared spectra of chlorpheniramine N-cyclohexylsulfamate (upper section) and an equimolar mixture of chlorpheniramine and N-cyclohexylsulfamic acid (lower section).

TABLE II —STABILITY OF CHLORPHENIRAMINE N-CYCLOHEXYLSULFAMATE IN AQUEOUS SOLUTION AT 50° FOR 2 MONTHS

pH	Original, mg./ml.	Two Months— mg./ml.	Appearance	% Loss
4	3.24	3.30	Clear	0
5	4.05	3.46	Clear	15
6	3.65	3.20	Clear	13
7	3.85	2.62	Sediment	32

SUMMARY AND CONCLUSIONS

1. The N-cyclohexylsulfamic acid salts of dextromethorphan and chlorpheniramine were prepared and characterized.

2. The salts were found to have greatly improved bitterness thresholds over that of the commonly occurring salts of the compounds.

3. When submitted to accelerated aging conditions, the compounds appeared to have good stability provided they were maintained at optimum pH levels.

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Influence of Kinetin and Gibberellic Acid on the Growth and Alkaloid Patterns in *Datura meteloides*

By DARRYL G. AMBROSE† and LEO A. SCIUCHETTI

Datura meteloides D.C. was administered four weekly-doses of 25 mcg. of kinetin (K) or gibberellic acid (GA). Different growth responses were induced by each treatment. Significant increases in height were noted in plants treated with GA whereas those treated with K were shorter than controls. Considerable increases in dry weights were noted in the GA-treated plants while reductions were observed in K-treated plants. The concentration of alkaloids in the organs of plants treated with GA was markedly reduced but no significant changes occurred with K. The total alkaloid content per plant was less in each of the treated groups but total stem alkaloids were greater in those treated with GA. The per cent of chlorophyll a and b was decreased by GA but increased by K.

PREVIOUS INVESTIGATIONS with kinetin, 6-(furfurylamino)-purine, and gibberellic acid (GA) indicate that these substances induce a profound effect on plant growth. Kinetin (K) was isolated and synthesized in 1955 by Miller, *et al.* (1, 2). This growth regulator has been shown to affect cell division (1, 3), cell enlargement as well as cell division (3, 4), root development (5, 6), shoot formation (7), and seed germination (8–10). Kinetin substituted for the light requirement of *Lemna minor* (11) and caused a modification of sporeling ontogeny in *Marsilea vestita* (12). K-treatment of lupin embryos *in vitro* caused about a twofold increase in alkaloid synthesis (13). Mothes, *et al.*, have shown that K affects nitrogen metabolism (14). Soluble nitrogen compounds in excised tobacco leaves were drawn from other leaf areas or added from the outside by K (14). A review of the literature has indicated that research has not been performed on the effects of K on the growth and alkaloid biogenesis in *Datura meteloides*.

The metabolic effects of GA on many plants (15–17), as well as on some medicinal plants (18), have been well established. The concentration of alkaloids in the plant organs was reduced and stem weight was increased in *Datura stramonium* (18–21), *Atropa belladonna* (19, 20), *Hyoscyamus niger* (22), and tobacco (23, 24). Increased height and variable results on leaftop, and root growth have been reported (18–24).

In view of the fact that K had not been employed on *Datura* species, it was decided to investigate the effect of this substance on the growth pattern, alkaloid formation, and chlorophyll content of *Datura meteloides*. It was further desired to ascertain whether this plant would respond to a GA treatment in a manner similar to that previously reported for *Datura stramonium*, and, also, to observe whether K and GA would induce similar metabolic effects.

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