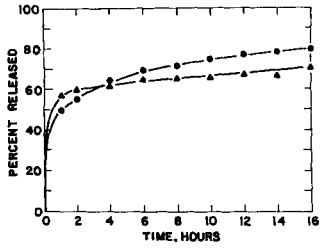

Fig. 4—Release of chlorpheniramine maleate from ethylcellulose-coated nonpareil seeds in 0.01 N HCl maintained at 37 ± 0.1°. Key: ●, miniature; ▲, 6-in. model.

TABLE IV—MINIATURE *Versus* 6-in. WURSTER CHLORPHENIRAMINE MALEATE TABLETS COATED WITH 1.25% ETHYLCELLULOSE SOLUTION

Expt. No.	1.22-in. Chamber	6-in. Chamber I	6-in. Chamber II
	% Release in 4 hr.		
1	54	18	17
2	33	18	14
3	50	17	33
4	46	36	31
5	60	51	50

cause the measurement of the release rates from 1.64 Gm. of seeds gives the average of a large number of individual assays, while the tablets were assayed individually. However, although the release rates are not precisely identical, the results do show that it should be possible to scale-up from the 1.22-in. coater to the 6-in. model with very little additional experimentation.

SUMMARY

An apparatus has been described which is capable of processing gram quantities of material in much the same manner as the larger 6-in. model Wurster unit. The miniature device has been evaluated and found to be highly versatile with respect to the types of discrete particles for which it can effect a continuous coating. Coating experiments indicate the miniature unit to be qualitatively comparable with the larger 6-in. model, although some quantitative differences were observed. The data suggest that minimal scale-up problems would probably accompany transition to the large unit.

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Keyphrases

Air-suspension coating apparatus, miniature
Coating apparatus—schematic diagram
Ethylcellulose–coating solution
Cellulose acetate phthalate–coating solution
Tablet coating
Capsule coating
Enteric dosage forms–coating
Drug release–coated dosage forms

Notes

Pharmacology and Toxicology of Potassium Perrhenate and Rhenium Trichloride

By THOMAS J. HALEY and FRANK D. CARTWRIGHT

A pharmacologic and toxicologic investigation of potassium perrhenate and rhenium trichloride showed that these compounds exhibited the same delayed acute toxicity previously reported for other rare elements. Rhenium trichloride was 10 times more toxic than potassium perrhenate but the latter compound was among the least toxic of all of the rare inorganic compounds studied. Potassium perrhenate was not irritating to the eyes and rhenium trichloride produced only a minimum of such irritation. Neither compound was irritating to the skin. Potassium perrhenate had no effect on isolated intestine while the liberation of acid from rhenium trichloride caused an intestinal spasm. Potassium perrhenate caused death by cardiovascular collapse coupled with respiratory failure. The compound also affected the superior cervical ganglion. Decomposition of aqueous solutions of rhenium trichloride and their extreme acidity prevented any pharmacodynamic studies.

IN 1933, HURD *et al.* (1) reported that they were unable to determine the LD_{50} for $KReO_4$ in mice or rats. They found wide distribution of the chemical in body tissues of the rabbit but no pharmacological effects in the dog. In 1940, Maresh *et al.* (2) reported that the i.p. lethal range for Re metal, given as $NaReO_4$, was 900–1,000 mg./Kg. for rats. Symptoms of toxicity included: cyanosis, increased respiration, and tonic convulsions. Rhenium trichloride was very toxic but the LD_{50} was not determined. Rhenates had no effect on the

Received September 2, 1966, from the Laboratory of Nuclear Medicine and Radiation Biology, Department of Biophysics and Nuclear Medicine, University of California School of Medicine, Los Angeles, CA 90007
Accepted for publication September 30, 1966.
These studies were supported by contract AT(04-1)GEN-12 between the Atomic Energy Commission and the University of California.
Preliminary report: *The Pharmacologist*, **8**, 225(1966).

hemogram of rats. The chemicals did cause a transient tachycardia and a slight hypotension in dogs. Inasmuch as this is the total information on the biological effects of perrhenates and rhenium trichloride and because the element and its compounds are coming into greater usage (3), the authors have re-evaluated the pharmacological and toxicological properties of $KReO_4$ and Re_2Cl_6.

METHODS

The samples of potassium perrhenate ($KReO_4$) and rhenium trichloride (Re_2Cl_6) had a minimum purity of 99.9%. The intraperitoneal LD_{50}'s were obtained with male CFl mice weighing 21 to 34 Gm.

The method of Draize *et al.* (4) was used to study eye and skin irritation in rabbits. In the eye irritation studies, two rabbits were used, and each animal had one eye exposed to 3 mg. of crystalline compound while the other eye served as a control. The rabbit skin irritation studies used six animals per compound and 0.5-Gm. amounts of each salt were applied.

The effects of the compounds on guinea pig ileal strips bathed in Ringer-Locke solution were studied in a thermostatically regulated 25-ml. bath using the Trendelenburg (5) method. Studies were also made on the isolated rabbit ileum in the presence of either 2.5 mcg. of acetylcholine or 0.5 mcg. of nicotine.

For the study of the effects of intravenous administration of these compounds, 15 cats of both sexes, weighing 2.3 to 4.6 Kg. were anesthetized with 0.5 ml./Kg. of allobarbital[1] urethan solution intraperitoneally. A six-channel recorder with transducers was used to record carotid arterial pressure, respiration, nictitating membrane contraction, ECG lead II, femoral arterial pressure, and femoral arterial flow. The latter was obtained with a 25-ml. flowmeter (6). Preganglionic stimulation of the cervical sympathetic fibers and the contralateral vagus fibers was accomplished with a stimulator at 8 v./10 sec. One hour was allowed to elapse prior to beginning drug administration. Intravenous dosages of the drugs used were: potassium perrhenate, 10–90 mg./Kg.; potassium chloride 10–140 mg./Kg.; rhenium trichloride, 10–20 mg./Kg.; hydrochloric acid, 1 ml. of 7.5, 15, and 30%; epinephrine, 5 mcg./Kg.; acetylcholine, 5 mcg./Kg.; histamine, 2 mcg./Kg.; and atropine, 2 mg./Kg. All injections were made at a constant volume of 1 ml., except at the highest doses where solubility dictated the total volume injected. Where appropriate, the results were analyzed statistically by the method of Litchfield and Wilcoxon (7).

RESULTS

Acute Toxicity—The LD_{50}/7 days for $KReO_4$ was 2.8 Gm./Kg. with a range of 2.5 to 3.05 Gm./Kg.; slope value was 1.07 (1.06–1.08). Toxic symptoms were sedation and severe ataxia with death or recovery within 7 days. No convulsions were observed. The LD_{50}/7 days for Re_2Cl_6 was 280 mg./Kg. with a range of 264.4 to 296.5 mg./Kg.; slope value was 1.1 (1.08–1.13). Toxic symptoms were sedation and abdominal irritation with death or recovery within 7 days.

Eye Irritation—Potassium perrhenate caused no detectable damage to the cornea, iris, or conjunctiva throughout the 72-hr. observation period. Rhenium trichloride caused an immediate irritation of the cornea, congestion and swelling of the iris, redness of the conjunctiva, and a very slight lacrimal discharge. However, all these ocular effects cleared up within 24 hr. and no permanent damage resulted from the exposure.

Skin Irritation—Neither potassium perrhenate nor rhenium trichloride had any effect on abraded or unabraded rabbit skin but the latter compound interacted with the hair to produce a permanent black stain. Similar staining was also observed on human skin and was probably caused by deposition of the metal on skin proteins.

Effects on Isolated Ileum—Potassium perrhenate in the dosage range of 2.4 to 952.4 mcg./ml. had no effect on the tonus or contractility of the isolated rabbit ileum and did not block the responses to either acetylcholine or nicotine. Similar results were obtained on the Trendelenburg guinea pig enteric ganglia preparation. Within the dosage range of 0.24 to 2.14 mg./ml., rhenium trichloride had no effect on the isolated rabbit ileum but at a dose of 2.38 mg./ml. the compound decomposed and the ileum went into spasm from the acid liberated.

Pharmacological Effects—Doses of 10–50 mg./Kg. of $KReO_4$ produced a transient hypertension with tachycardia but had no effect on respiration. Hypotension and bradycardia as well as bradypnea occurred at doses of 60 and 70 mg./Kg. Atropinization did not affect the above responses but did increase the toxic dose by 10 mg./Kg. Femoral blood flow decreased at doses of $KReO_4$ of 40 to 70 mg./Kg. and atropinization shifted the responses to doses of 60 to 80 mg./Kg. Death from cardiovascular collapse coupled with respiratory failure occurred in 4 of 5 cats at 70 mg./Kg. and atropinization increased the dosage to 80 mg./Kg. for three cats and 90 mg./Kg. for the other two animals. Electrocardiographic changes caused by $KReO_4$ included: elevated P-waves, bradycardia, dropped beats, absent P-waves, absent T-waves, increased S-T interval ventricular tachycardia, transient auricular fibrillation, transient ventricular fibrillation, and 2 to 1 heart block. Atropinization had no influence on the cardiac changes produced by the chemical. $KReO_4$ did not block the pharmacological responses to acetylcholine, epinephrine, or histamine. Control studies with KCl indicated that the K^+ ion contributed little or nothing to the responses obtained with $KReO_4$ because KCl required 110 to 120 mg./Kg. to affect the cats, whereas $KReO_4$ produced its effects at much lower doses.

$KReO_4$ caused contraction of the nictitating membrane of the nonatropinized preparations but not of the atropinized ones, indicating a direct effect on the superior cervical ganglion because the responses resembled those obtained with acetylcholine and electrical stimulation rather than an epinephrine response and because atropine blocks at the ganglionic synapse.

Rhenium trichloride produced a slight hypertension at a dose of 10 mg./Kg. and was lethal to the cat when 20 mg./Kg. was given. However, these effects were related to the acid liberated by decomposition of the Re_2Cl_6 and were duplicated by the administration of the same concentration of hydrochloric acid to a control animal.

[1] Trademarked as Dial by Ciba Pharmaceutical Co., Inc., Summit, N. J.

DISCUSSION

The low order of toxicity of potassium perrhenate (1) and the high order of toxicity of rhenium trichloride (2) have been confirmed and extended to determination of their intraperitoneal LD_{50}'s. The rhenium compounds tested showed no real irritating properties on the eyes or skin of animals and no effects on isolated intestine. This is a striking contrast to observations on other rare elements (8–10). The chemical composition of the rhenium compounds, their solubility, and their rate of decomposition determines their lethality to animals. Rhenium trichloride, which decomposes readily with the liberation of hydrochloric acid, was 10 times more toxic than potassium perrhenate.

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Keyphrases

Potassium perrhenate—pharmacology, toxicology
Rhenium trichloride—pharmacology, toxicology
LD_{50}—potassium perrhenate, rhenium trichloride
Eye irritation
Skin irritation
Ileum, isolated–effect on tonus, contractility

Photodisintegration Studies of ^{14}C-Carboxyl 2,3,5-Triiodobenzoic Acid

By R. H. JARBOE, JR., J. B. DATA, and J. E. CHRISTIAN

^{14}C-Carboxyl labeled 2,3,5-triiodobenzoic acid was examined at various intervals of time during exposure to ultraviolet irradiation. Photodisintegration occurred and the amount of degradation increased in quantity with increased duration of exposure. 2,5- and 3,5-diiodobenzoic acid were identified as two products resulting from the irradiation. Other unidentified products are also present.

IN CERTAIN PLANTS 2,3,5-triiodobenzoic acid (TIBA) has pronounced hormonal effects on the flowers, fruits, yields, metabolism, and translocation of natural plant constituents (1–8). Because these plants serve as a source of food to man or indirectly by first serving as food for animals which ultimately constitute man's diet, the question naturally arises as to the safety of this material to man. Furthermore, when TIBA is used on plants, it could be questioned whether the photodisintegration products from TIBA might be a health hazard. If sunlight causes photochemical deterioration either before or after absorption in the plant, the products of degradation could be translocated throughout the plant and eventually, directly or indirectly, become incorporated in foods.

EXPERIMENTAL

Materials—Glass chromatographic plates, 20 × 20 cm., utilizing silica[1] of 250 μ thickness, were used. A plastic preservative for thin-layer chromatograms, Brinkmann Instruments Co., Westbury, L. I., N. Y. was used.[2] The ultraviolet source (Ultra-Violet Products, Inc., South Pasadena, Calif., long-wave UV model S1 3660) was equipped with a long wavelength filter to approximate normal sunlight. The samples were counted in a Packard model 3003 Tri-Carb liquid scintillation spectrometer. The solvent system used was composed of a ratio of 10 parts of petroleum ether (b.p. 30–60°) and 1 part of propionic acid. Solvents and chemicals used in this study were of reagent grade or their equivalent.

Purification of TIBA-^{14}C—TIBA labeled in the carboxyl position with ^{14}C (9) was purified utilizing thick-layer chromatographic techniques prior to the photodisintegration studies. The purification procedure consisted of pipeting an alcoholic solution of approximately 93% TIBA-^{14}C onto previously prepared 1-mm. silica plates and air dried. The plates were developed in a solvent system of petroleum ether–propionic acid in the ratio of 10 parts of petroleum ether (b.p. 30–60°) and 1 part of propionic acid and subsequently exposed to photographic film (Eastman Kodak No Screen medical X-ray film). The resultant autoradiogram was used to identify TIBA-^{14}C. The TIBA-containing silica was scraped from the plate and placed in a Soxhlet extractor and extracted with anhydrous ether for a period of 72 hr. The Soxhlet extractor was wrapped with black paper to protect the contents from exposure to light. After the extraction period the ethereal solution was then concentrated to dryness under reduced pressure without heat in the dark.

Photochemical Degradation of TIBA-^{14}C—The TIBA-^{14}C used for the preparation of 30 ml. of a 2.1 × 10^{-2} % aqueous suspension was the same as that used in a study conducted on field grown soybeans by Spitznagle (9). About 5 ml. of the suspension was

Received May 29, 1967, from the Departments of Bionucleonics and of Medicinal Chemistry, School of Pharmacy and Pharmacal Sciences, Institute for Environmental Health, Purdue University, Lafayette, IN 47907
Accepted for publication September 15, 1967.
This investigation was supported in part by a grant from the International Minerals and Chemical Corp., Skokie, Ill.
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[2] Neaton