Absorption of ^{3}H-Benzocaine from Ointments following Rectal Administration in Rats

JAMES W. AYRES ˣ, DUANGCHIT LORSKULSINT, and ALBERT LOCK

Abstract □ Total radioactivity in the blood of rats for 5 hr following rectal administration of ^{3}H-benzocaine in oleaginous, absorption, emulsion (water-in-oil and oil-in-water), and water-soluble ointment vehicles was measured. The release was greatest from the water-soluble vehicle and followed the same relative order as seen in an earlier *in vitro* experiment. No intact benzocaine was found in the blood using radiochromatography. *In vitro* hydrolysis of benzocaine by rat blood did not occur as determined with the techniques of this experiment.

Keyphrases □ Benzocaine—absorption from ointments, rectal administration, rats □ Anesthetics, local—benzocaine, absorption from ointments, rectal administration, rats □ Ointments—benzocaine absorption, rectal administration, rats

Benzocaine (ethyl *p*-aminobenzoate) is an extensively used local anesthetic, commercially available in semisolid dosage forms in concentrations varying from 0.5 to 20%. Different vehicles are used in the multitude of products listing benzocaine as an active ingredient. The *in vitro* release of benzocaine from oleaginous, absorption, emulsion (water-in-oil and oil-in-water), and water-soluble ointment vehicles through a cellulose membrane to an aqueous sink was recently studied (1). It was shown that vehicle composition markedly affected the rate of release of the active ingredient.

Benzocaine is often included in hemorrhoidal products for the treatment of pain and pruritis. The drug must leave the vehicle and pass into the mucous membranes in order to act as a local anesthetic by blocking nerve conduction. After penetration, the drug is removed from the rectal tissues *via* the hemorrhoidal veins. The lower hemorrhoidal veins bypass the liver and carry absorbed drug directly into the general circulation; the upper hemorrhoidal vein connects with the portal vein leading to the liver (2).

The rate of appearance and amount of drug in the blood after rectal application should be a useful measure of the rate and amount of drug transfer from a dosage form to the sensory nerve endings in the rectal mucosa. Absorption of some local anesthetics has been reported to be dependent on the mucous surface involved (3). The rate of absorption largely depends upon the blood supply to the tissue (4).

The absorption of detectable amounts of benzocaine after application to abraded abdominal skin in dogs (3) and the ability of various benzocaine-containing preparations to obtund the itch and burning of electrical stimulation in humans (5) were reported. No comparisons of absorption of benzocaine from various formulations of semisolids through mucous membranes have been published.

The metabolic fate of local anesthetics has important clinical significance (4), but no metabolic studies of benzocaine have been reported. It may, however, follow the metabolic pathways of procaine (6, 7), which is also a local anesthetic ester. Although detoxification of most local anesthetics is accomplished almost entirely by the liver (4), procaine is rapidly hydrolyzed in human plasma. The enzymes involved are nonspecific (4) and hydrolyze different local anesthetics at various rates. For example, piperocaine was hydrolyzed 6.1 times faster than procaine, and tetracaine was hydrolyzed only 0.22 times as fast as procaine (7).

Hydrolysis of the local anesthetics in the plasma of laboratory animals was shown to be very slow (8) and dependent on the animal plasma used. In another experiment using isolated, perfused rat liver, procaine was not hydrolyzed in the rat blood but was hydrolyzed by the liver (9). Hydrolysis studies of benzocaine by the enzymes in rat blood have not been reported.

The purposes of the present investigation were to: (*a*) compare the effects of various ointment bases, with markedly different physical–chemical properties, on the rate of release of benzocaine after rectal administration in rats; (*b*) relate these results to a previously reported *in vitro* study (1); and (*c*) investigate the stability of benzocaine in whole rat blood *in vitro*.

EXPERIMENTAL

Reagents and Equipment—^{3}H-Benzocaine[1] (general label) was used as obtained. An internal standardization method was used to determine the activity of the drug as 0.067 mCi/mmole. A liquid scintillation spectrophotometer[2] was used to count all samples.

Other reagents and equipment used were: dioxane[3] (scintilAR), naphthalene[3] (purified), 70% perchloric acid[3], 30% hydrogen peroxide[3], benzene[3], dioxane[3], 2,5-diphenyloxazole (scintillation grade)[4], 1,4-bis[2-(4-methyl-5-phenyloxazolyl)]benzene (scintillation grade)[4], polyethylene glycol 1000[5], polyethylene glycol 4000[5], white petrolatum[6], pentobarbital sodium[7], heparin sodium injection[8] (1000 USP units/ml), polyethylene tubing[9], commercial fluor[10], acetic acid[11], chromatographic plates[12], absorption vehicle[13], water-in-oil emulsion[14], and oil-in-water emulsion[15].

Pharmacology—Female Sprague–Dawley rats, 100–280 g, were

[1] Calatomic, Los Angeles, Calif.
[2] Packard Tri-Carb liquid scintillation spectrometer model 2405 or 3375, Packard Instrument Co., Downers Grove, Ill.
[3] Mallinckrodt Chemical Works, St. Louis, Mo.
[4] Packard Instrument Co., Downers Grove, Ill.
[5] J. T. Baker Chemical Co., Phillipsburg, N.J.
[6] Matheson, Coleman and Bell, Los Angeles, Calif.
[7] City Chemical Corp., New York, N.Y.
[8] Eli Lilly Co., Indianapolis, Ind.
[9] Clay Adams, New York, N.Y.
[10] Omnifluor, New England Nuclear, Boston, Mass.
[11] Dupont.
[12] Uniplate (precoated with silica gel GF, 250 μm), Analtech, Inc.
[13] Aquaphor, Duke Laboratories, South Norwalk, Conn.
[14] Aquaphor–water (1:1).
[15] Neobase, Burroughs Wellcome and Co., Research Triangle Park, N.C.

used. Pentobarbital sodium (55 mg/kg ip) was used for induction and maintenance of general anesthesia. The trachea was intubated [polyethylene tubing, 0.139 cm (0.055 in.) i.d., 0.191 cm (0.075 in.) o.d.] to facilitate respiration. A midventral incision was made into the abdominal cavity extending from the xyphoid process to the midabdominal region. The inferior vena cava was cannulated [polyethylene tubing, 0.076 cm (0.030 in.) i.d., 0.122 cm (0.048 in.) o.d.], and the abdominal incision was closed with wound clips.

The ointments were inserted rectally from a U-80 insulin syringe with the barrel cut off at the 10-U mark. The dosage form was followed by a short, blunt, glass rod, which served as a plug to prevent leakage. A 0.1-ml blood sample was withdrawn *via* the inferior vena cava cannula before the drug was inserted and at 5, 10, 20, 40, 60, 90, 120, 240, and 300 min after insertion.

A 0.1-ml heparinized normal saline solution (7.5 units of heparin/ml) was injected through the cannula immediately after each blood sample was obtained. All blood samples were placed directly into the counting vials. When necessary, additional pentobarbital sodium (2.75 mg/kg ip) was injected to maintain anesthesia.

Sample Analysis—Total radioactivity in each blood sample was determined using a wet oxidation method (10) as follows. First, 0.1 ml of blood was placed in each counting vial. Then 0.2 ml of 70% perchloric acid was added to each sample vial for digestion, and the contents were agitated until the acid was well mixed with the sample. Then 0.4 ml of 30% hydrogen peroxide was added, and the contents were mixed again.

The vial was tightly capped to minimize evaporation of fluid during digestion and then placed in a water bath at about 70° for 60 min or until the contents of the vial became clear and colorless. After the samples were cooled, 8 ml of 2-methoxyethanol and 10 ml of toluene scintillation solution were added. The vial was capped and shaken, and a clear solution was formed.

The toluene scintillation solution consists of 4 g of a commercial fluor[10] in enough toluene to make 1 liter. All samples were counted on a liquid scintillation spectrometer[2] using the ^3H quick set and a preset time of 10 min. The counting efficiency was determined by use of external standardization (AES ratio).

Metabolism—TLC was used to separate radioactive benzocaine from its metabolites after rectal administration of 20% ^3H-benzocaine in polyethylene glycol. At 30, 60, 120, 180, 240, and 300 min, 0.1 ml of blood was withdrawn through the cannula, immediately placed in a small test tube containing 1 drop of 50% sodium arsenite solution and 1 drop of 10% saponin solution, and mixed well. The sample was then spotted on commercially available plates[12] and developed (11) in benzene–dioxane–acetic acid (90:75:8).

After solvent evaporation, the plate was examined under UV light for spot separation. Then the entire chromatographic band, from the origin to the solvent front, was divided into 1-cm successive zones, and the adsorbent of each zone was removed with a razor blade and placed in counting vials. 2-Methoxyethanol (8 ml) and commercial fluor[10] (10 ml) in toluene scintillation fluid were added and mixed. After the adsorbent completely settled in the bottom of the vials, each vial was counted for 10 min.

For the *in vitro* study of benzocaine hydrolysis, 2 ml of blood was freshly withdrawn from the inferior vena cava of the rat and placed in a 10-ml beaker containing 1 drop of heparin solution (1000 units/ml). Two drops of ^3H-benzocaine solution (50 mg/ml in alcohol) were added. At 0, 5, 30, and 60 min, 0.1 ml of blood was taken from the beaker and immediately placed in a test tube. The tube contained 1 drop of 50% sodium arsenite solution to inhibit enzyme activity (6) and 1 drop of 10% saponin solution to lyse the red blood cells, and the solution was mixed well.

The sample was then spotted as a row of small spots on a 10 × 20-cm precoated thin-layer plate[12] and developed with the three-component solvent system. The chromatoplates were examined under UV light to locate the benzocaine and its metabolites. The plates were divided and counted as already described. The same procedure was repeated with a saturated solution of ^3H-benzocaine in water and 50 mg of ^3H-benzocaine/ml in polyethylene glycol 4000. The blood was analyzed after 60 min only in the latter study, and the blood was maintained at 37° in a water bath.

Dosage Form Preparation—^3H-Benzocaine was incorporated in the vehicle with the use of a spatula and an ointment slab by geometric dilution. The ointment was loaded into a plastic disposable U-80 insulin syringe and stored for no more than 1 week in the refrigerator. The end of the syringe was cut off at the 10-U mark, and the contents were inserted directly from the modified syringe into the rectal cavity.

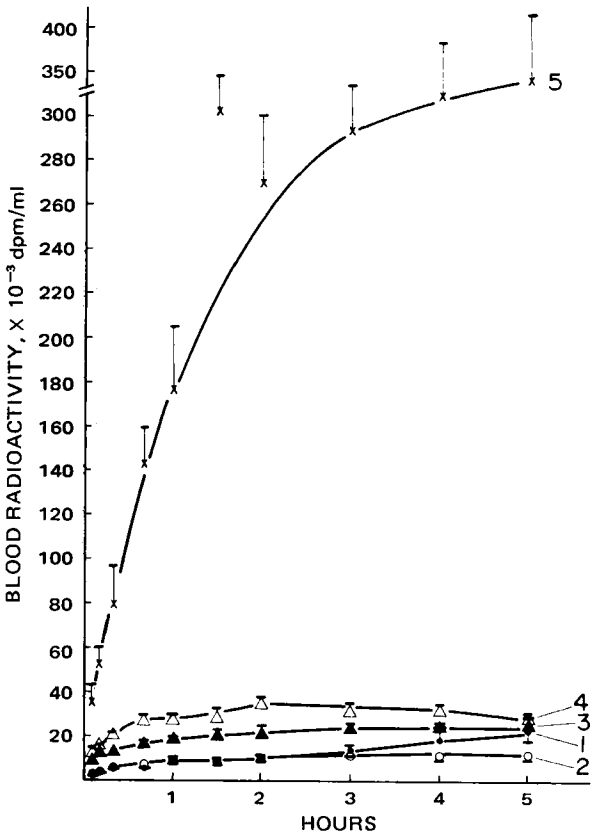

Figure 1—*Blood radioactivity after the application of 20% ^3H-benzocaine in different ointment vehicles. Key: 1, white petrolatum; 2, absorption vehicle; 3, water-in-oil emulsion; 4, oil-in-water emulsion; and 5, polyethylene glycol. The standard error of the mean is shown on one side of each point.*

RESULTS AND DISCUSSION

The rectal absorption in rats of radioactivity from 20% ^3H-benzocaine in five different ointment bases (white petrolatum, absorption vehicle, oil-in-water emulsion, water-in-oil emulsion, and water-soluble vehicle) was compared. The means of at least five animals for each formulation are shown in Fig. 1. The results of a point-by-point comparison of the means obtained at each sample time was made using the Student *t* test.

The experimental values obtained were significantly different (95% confidence level) for almost every sample time when comparing all products except Formulation 1 *versus* 2. Statistical analysis using an unequal variance technique showed that less than 5% of the variation in blood level radioactivity among different rats receiving different formulations was due to rat weight variation. No pharmacokinetic analysis was attempted since total radioactivity was measured and the method is not specific for benzocaine.

In fact, as will be seen later, no intact benzocaine was detected *in vivo*, and the radioactivity represents metabolized drug. However, total radioactivity can be used to indicate the relative rate of absorption of the drug from the various formulations, since all radioactivity in the blood originated as intact radioactive drug in the dosage forms.

For a drug to be absorbed from the rectum, it must be released from the vehicle and be distributed through the surrounding fluids where it is absorbed through the rectal mucosa. The rectum contains fluids in which water-soluble vehicles can dissolve. However, the quantity of this fluid is not sufficient to effect rapid dissolution of a suppository (12).

The release of drug from the suppository vehicle depends on the relative affinities of drug for the vehicle and the rectal fluid. Low affinity of the drug for the vehicle or ready solubility of drug in the

aqueous rectal fluid favors rapid release of drug. Conversely, high affinity of drug for the vehicle and poor drug solubility in aqueous rectal fluid decrease the rate of released drug (13). Benzocaine is known to have a low affinity for, or a low solubility in, aqueous fluids.

The five types of vehicles chosen for this experiment represent a wide range of physical–chemical properties and relative affinities for benzocaine. The relative release profiles in Fig. 1 show that the semisolid polyethylene glycol solution released the drug much more rapidly than the semisolid suspensions, even though the polyethylene glycol vehicle has a much greater affinity for the drug than the other vehicles. These results support the contention that one primary rate-limiting step in drug absorption from suppositories is the partitioning of the dissolved drug from the vehicle rather than the dissolution of the drug in the body fluids (2).

Although it is desirable that the partition coefficient of the drug favor solubility in the rectal fluids rather than in the vehicle, a drug that is very insoluble and suspended in the vehicle will be absorbed slowly due to the small concentration of dissolved drug available to partition into the rectal fluid. It follows that the onset of the local anesthetic action of benzocaine applied rectally as a suspension is likely to be slower and perhaps less intense than when applied as a solution, even though the solubilizing vehicle may have a relatively high affinity for the drug. Theoretically, the suspensions will continue to release the drug over a longer time period than the polyethylene glycol solution, but this has no significance during the first 5 hr and the significance beyond that time is unknown (Fig. 1). The relative release rates *in vivo* are in agreement with an earlier *in vitro* study (1) which measured the relative release rates of benzocaine from these vehicles.

When the radioactivity of a sample is counted, the total radioactivity is the sum of the total number of radioactive molecules of any chemical form in the sample. Generally, each metabolite formed from the drug has its own rate of formation, rate of elimination, and volume of distribution and their pharmacokinetic parameters are different from each other and from the original drug. Therefore, a thin-layer radiochromatographic method of separating benzocaine from its metabolites was investigated to determine if the total radioactivity was due to intact ^{3}H-benzocaine.

Procaine, which is structurally similar to benzocaine, has been reported (6) to be rapidly hydrolyzed by human serum cholinesterase and rat liver (9) to *p*-aminobenzoic acid. Since hydrolysis of benzocaine would also lead to *p*-aminobenzoic acid, a TLC system (11) that separated benzocaine (R_f 0.85) from *p*-aminobenzoic acid (R_f 0.70) was chosen. The R_f values of both substances were high enough to leave room to detect more polar metabolites, since *p*-aminobenzoic acid is reported to be converted to various polar conjugates (6, 11).

Periodic blood samples were collected to measure the *in vivo* degradation of benzocaine. The 30-min blood sample did not show any radioactivity above background in the zone where benzocaine should be located. The counts were high in the zone where the R_f value was approximately 0.70, the R_f value of *p*-aminobenzoic acid. For the 60-, 120-, 180-, 240-, and 300-min samples, the R_f value of the zone where the highest count was located was approximately 0.60–0.66. Another radioactive zone with an R_f value of 0.40–0.50 was present. The R_f values obtained in this study can only be approximations, because the exact positions of the spots could not be determined using scintillation. Oxidation of the silica gel to release absorbed radioactive molecules increased the counts but did not provide any further information concerning the hydrolysis of benzocaine.

The possibility that the prolonged blood level of radioactivity (Fig. 1) was due to formation of tritiated body water due to exchange of ^{3}H from the drug or its metabolites was ruled out in the following manner. Whole blood (1.0 ml) collected at different times from five rats was treated with 1 drop of 10% saponin solution to lyse the red blood cells and microdistilled at atmospheric pressure to collect 0.1 ml of aqueous material. The distillate contained less than 8% of the radioactivity of an equal volume of whole blood, indicating that little or none of the radioactivity in whole blood was due to tritiated water formed by exchange with the tritiated drug or its metabolites. From these results, it is probable that benzocaine is hydrolyzed *in vivo* in rats to *p*-aminobenzoic acid, which is then further metabolized.

An attempt was made to determine if benzocaine was being hydrolyzed by blood enzymes in the rat. Various amounts of ^{3}H-benzocaine in different solvents (see *Experimental*) were introduced into heparinized blood. At specified time intervals, the blood enzymes were inactivated, the cells were lysed, and the samples were chromatographed. The chromatoplates were scraped off and counted in a liquid scintillation spectrometer, but the distribution of the total radioactivity was not well delineated. Some zones on the plate, below the benzocaine zone, did show slightly higher counts than background but represented an extremely small amount of, if any, metabolites. Scintillation counting showed much higher counts than background only in the zone for benzocaine as detected with UV light.

Therefore, no *in vitro* hydrolysis of benzocaine was found with the method used in this study. The reason could be that (*a*) benzocaine is not hydrolyzed in rat blood, (*b*) the enzyme was inactive under the *in vitro* conditions utilized, or (*c*) the method used was not sensitive enough to detect the amount that was hydrolyzed. The first reason for the results is the most probable (7, 8). Benzocaine is clearly degraded *in vivo*, however, and the degradation probably occurs in the liver (9).

CONCLUSIONS

1. The rectal absorption and blood concentration of total radioactivity in rats following insertion of ^{3}H-benzocaine in various ointment vehicles were determined.

2. The total radioactivity absorbed rectally from the vehicles was in the following decreasing order: polyethylene glycol > oil-in-water emulsion > water-in-oil emulsion > absorption base and white petrolatum. The absorption base and white petroleum did not give significant differences in the blood level curves.

3. Relative *in vivo* results for the formulations studied here correlated well with results of an *in vitro* method reported earlier.

4. No intact benzocaine was found in the blood at the time periods studied following rectal administration of the drug.

5. *In vitro* hydrolysis of benzocaine by whole rat blood was not found. More research is needed to determine the mechanism of benzocaine degradation.

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[x] To whom inquiries should be directed.

Synthesis of 2-Pyridyl-α-toluenesulfonates as Antimalarials

M. HAMER [x], O. F. BATZER, M. J. MOATS, C. C. WU, and E. P. LIRA

Abstract □ A series of substituted 2-pyridyl-α-toluenesulfonates was synthesized for antimalarial testing. They were prepared by treating various 2-pyridinols with α-toluenesulfonyl chlorides in the presence of an alkali. In tests against *Plasmodium berghei* in mice at 640 mg/kg, only 3,5-dichloro-2-pyridyl-α-toluenesulfonate was considered active, *i.e.*, doubled the mean survival time.

Keyphrases □ 2-Pyridyl-α-toluenesulfonates—synthesis, screened for antimalarial activity □ Antimalarials, potential—synthesis and screening of 2-pyridyl-α-toluenesulfonates

Some time ago, a series of alkanesulfonate esters of variously substituted 2-pyridinols was prepared in these laboratories (1). In connection with this earlier study, some α-toluenesulfonates also were prepared. One of these, 3,5-dichloro-2-pyridyl-α-toluenesulfonate (I), was found to be active against *Plasmodium berghei* in mice. The mean survival time (MST) for mice treated with I at 640 mg/kg was 15.8 days; for controls, it was 6.1 days. Consequently, a series of substituted 2-pyridyl-α-toluenesulfonates was prepared for antimalarial testing[1].

DISCUSSION

These compounds were prepared mainly by treatment of a 2-pyridinol[2] with an α-toluenesulfonyl chloride in toluene at 25° in the presence of a small excess of triethylamine (Scheme I). The yields were generally in the range of 30–90%. In two instances, the insolubility of the pyridinol in the toluene and triethylamine mixture necessitated the use of 1% KOH or 1% NaOH in the Schotten–Baumann procedure (Table I, XXV and XXIX).

Sulfonylation of the 2-pyridinols occurred at the oxygen in all but one case. The single exception was the product from the reaction of 5-carbethoxy-3-chloro-2-pyridinol with α-toluenesulfonyl chloride. The insolubility of this pyridinol also required the use of 1% KOH. In this case, only the *N*-substituted product was isolated, as evidenced by its IR and UV spectra (see *Experimental*).

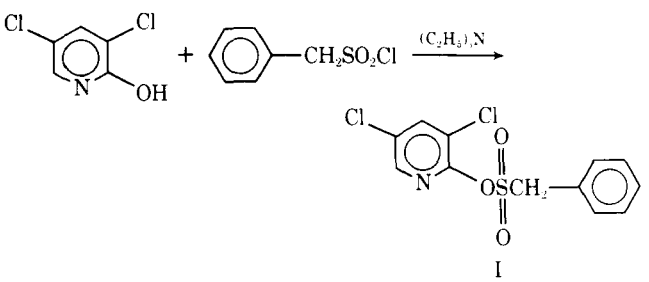
Previous work from these laboratories showed that the products from the reaction of various 2-pyridinols with alkanesulfonyl chlorides gave exclusively sulfonate esters (1). When various arenesulfonyl chlorides were used with a specific 2-pyridinol, 3,5-dichloro-2-pyridinol, both *O*- and *N*-sulfonated products resulted (2) in each case.

Four of the 2-pyridinols employed have not previously been reported (Table II). The product resulting from the chlorination of 3-methoxy-2-pyridinol at 25° in 10% hydrochloric acid (Table II, XXXII) proved to be the 6-chloro isomer, as evidenced by its NMR spectrum. Chlorination of 4-methyl-2-pyridinol [from diazotization and hydrolysis (3) of 2-amino-4-picoline] gave the previously unreported 3,5-dichloro-4-methyl-2-pyridinol (Table II, XXXIII). The intermediate 5-carbethoxy-3-chloro-2-pyridinol (Table II, XXXIV) was synthesized *via* chlorination of the reported (4) 5-carbethoxy-2-pyridinol. Attempts at chlorinating the acid (6-hydroxynicotinic acid) prior to esterification were unsuccessful.

The reported 5-chloro-3-methyl-2-pyridinol (5) was obtained by chlorination of 3-methyl-2-pyridinol. However, when 5-methyl-2-pyridinol was chlorinated under the same conditions in an attempt to prepare the 3-chloro derivative, a semisolid was obtained which could not be purified by distillation or recrystallization without decomposition. This material gave a positive test for an active halogen with alcoholic silver nitrate, and treatment with dilute sodium hydroxide at 25° gave an intensely dark-violet solution within 5 min.

The known 3,5-dichloro-6-methyl-2-pyridinol (5) was prepared from 3-methyl-2-pyridinol. Chlorination (5) or bromination (6) of 2-pyridinol at room temperature in dilute mineral acid gave the 3,5-dihalo product in good yield; the 3,5-dinitro intermediate was obtained on treatment of 2-pyridinol with fuming nitric and sulfuric acids at 80° (7). Similarly prepared were the 3,5- and 5,3-chloronitro-2-pyridinols (8).

The α-toluenesulfonyl chlorides were prepared by treatment of the appropriate chloromethylbenzene with sodium sulfite in refluxing 50% aqueous ethanol, and the sodium α-toluenesulfonates thus obtained were treated with refluxing phosphorus oxychloride (Table III). This method worked fairly well with those chloromethylbenzenes that contained electronegative halogen groups. However, in the two cases where electron-donating methyl groups were present (Table III, XLI and XLII), the sodium salts were converted back to the original benzyl chlorides, instead of the expected sulfonyl chlorides, on treatment with refluxing phosphorus oxychloride. Presumably the sulfonyl chlorides formed and, activated by the 3- or 4-methyl, were displaced by a chloride ion. When the reactions were carried out with phosphorus oxychloride at a reduced temperature (60°), the desired 3- and 4-methyl-α-toluenesulfonyl chlorides were obtained. The unreported α-toluenesulfonyl chlorides prepared are listed in Table III. The known α-toluenesulfonyl chlorides utilized include: 2- and 4-chloro (9); 2,4- and 3,4-dichloro (9); 2-bromo, 3-chloro, and 2- and 3-fluoro (10); and 2,4,5-trichloro (11).



I

Scheme I

[1] Contract with the Walter Reed Army Institute of Research.

[2] Although the conventional name "2-pyridinol" is used throughout, spectroscopic evidence substantiates that the materials exist as the 2-pyridone (E. Spinner and J. C. B. White, *J. Chem. Soc. B*, **1966**, 991).