# Ultraviolet Absorption of Surface Anesthetics*

*By John C. Bird*†

While investigating surface anesthetic compounds of the class distinguished by their specific effect upon the sensory nerve endings, and characterized generally by the *p*-aminobenzoic acid configuration, the author at times observed a bright bluish fluorescence in alcoholic solution. This effect was shown particularly well by Larocaine (*p*-aminobenzoyl-2,2-dimethyl-3-diethylamino propanol) which, on closer observation using Corning glass filters (Corex Red Purple A 986 and Blue Fluorescing 014), was found, even in very low concentration, to arrest completely the passage of ultraviolet rays in the band 250 to 300 mμ.

Several of these compounds were then examined, using a quartz spectrophotometer with tungsten arc light source, a 1-cm. quartz cell, and 95% alcohol as solvent. Transmission factors at different wave lengths were measured and plotted as curves.

Marchlewski and Mayer (1), in studying the absorption spectra of di-substituted benzene derivatives, showed that the *para* compounds absorbed light to a much greater extent than either the *ortho* or *meta* derivatives. Characteristic curves were obtained, *inter alia*, for methyl-, nitro-, hydroxy- and aminobenzoic acids—Marchlewski's absorption curves for the latter being shown in Fig 1. It will be noted that the maximum absorption of the *para* compound is at about 2800 Å., the other lesser peaks being located toward the longer waves.

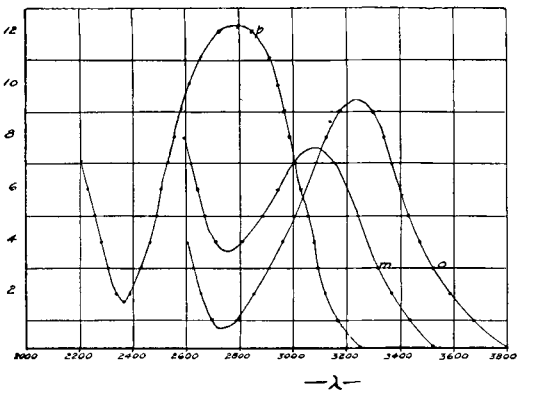



Fig. 1.—Absorption Spectra.
*o*, *m*, *p*-Aminobenzoic acids in water (Marchlewski).

## EXPERIMENTAL

Samples of the following derivatives of *p*-aminobenzoic acid were secured and purified when necessary by crystallization: ethyl- (Benzocaine), propyl-, isobutyl-, dibutylaminopropyl- (Butyn), diethylaminoethyl- (Procaine), and dimethyl-3-diethylaminopropyl- (Larocaine). The bases were obtained as required by precipitation of the hydrochloride or sulfate solutions with alkali, extraction with ether, drying and evaporation in the usual way. Butyn base was a viscous oil which did not solidify. Procaine and Larocaine gave oily products which slowly crystallized on standing.

The purified and dried substances were dissolved in 95% alcohol (1% concentration) and the solutions diluted again as required, usually to 0.01%.

Figure 2 shows the first group of curves for the ethyl-, propyl- and isobutyl-*p*-aminobenzoates. The curves vary only slightly and show complete absorption of light between about 250 and 320 mμ. The steeper portion of the curves indicates a fairly sharp cut-off at the higher limit with gradually increasing passage of light until 100% is passed over 400 mμ. The sharpest cut-off would seem to be that of the ethyl compound, although there is little to choose between them below 320 mμ. There are also secondary and smaller transmission "bands" having maxima at 242 mμ, at which about 10% of the light is passed. The position and characteristics of these bands appear the same in each case.

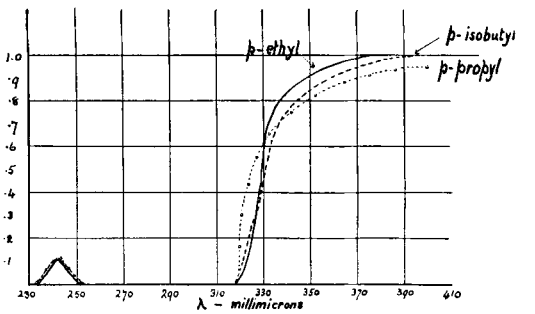



Fig. 2.—Transmission Spectra.
*p*-Aminobenzoates 0.01% in ethanol. $d$ = 1 cm.

Examination of more complicated structures (Procaine, Butyn and Larocaine) showed almost identical phenomena, a fairly steep cut-off at 320

* From Hoffmann-La Roche Inc., Nutley, N. J. Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

† Vick Chemical Company, New York, N. Y.

mμ and complete absorption of light down to 260 mμ (Fig. 3). The characters of the smaller transmission bands were, however, slightly different, Butyn passing the most (about 25%), Larocaine the least light (about 10%) at about 245 mμ. The general contours of the curves and limits of absorption (or transmission) of all six substances are, however, very similar.

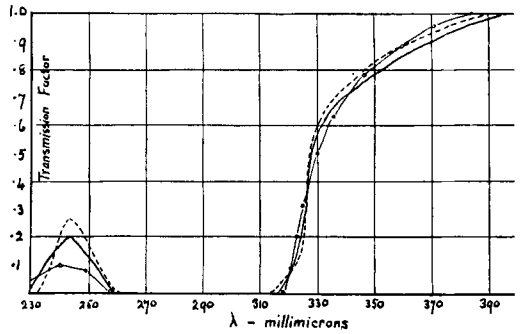



Fig. 3.—Transmission Spectra.
Procaine base —. Butyn base -----. Larocaine base—·—. 0.01% in ethanol. $d$ = 1 cm.

Certain salicylates have been found useful as light filters in the ranges mentioned, so the transmission curve of pure salicylic acid was determined (Fig. 4). The filtering effect is quite sharp in the range about 290 to 320 mμ, which includes the so-called erythema or blistering rays mainly responsible for the painful effects of sunburn. The "secondary" transmission band has a maximum at 260 mμ at which 50% of light of this wave length passes. It was therefore thought of interest to prepare and examine the salicylic acid salts of some of these anesthetic bases.

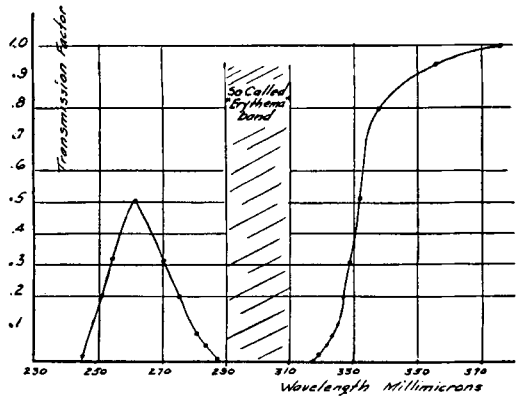



Fig. 4.—Transmission Spectrum.
Salicylic acid. 0.01% in ethanol. $d$ = 1 cm.

Salts of the lower molecular weight compounds (ethyl, isobutyl, etc.) were simply prepared by mixing strongly cooled aqueous solutions of the hydrochlorides of the bases and sodium salicylate in equivalent proportions.

Compounds of Larocaine, Butyn and Procaine were made by dissolving stoichiometric proportions of the reactants separately in cold, dry ether and adding the two solutions, whereupon the salicylates were precipitated.

*Larocaine Salicylate.*—Dissolve 139 Gm. of Larocaine base and 69 Gm. of pure salicylic acid separately in about 100-cc. portions of cold, dry ether (sodium), and add the two solutions. A milky white liquid is immediately formed, the precipitate rapidly becoming granular and finally forming a coarse coagulum. Stand in the refrigerator for several hours. Filter, wash with a little ether and dry, avoiding unnecessary exposure to light; yield, 200 Gm. The reactants and solvents should be dry, or the salicylates assume a somewhat sticky amorphous character, later becoming crystalline on standing in the cold.

Larocaine salicylate forms a white crystalline powder soluble in the cold in chloroform and acetone, slightly soluble in ether; soluble hot in alcohol and toluene; insoluble in carbon tetrachloride, benzene and petroleum ether. It dissolves in hot water and crystallizes readily on cooling in thick prisms, m. p. 135° C. Solubility in cold water is about 2%. The solid and its solutions are photosensitive, turning yellow to brown on exposure to light. Alkalies readily decompose it, reforming the base.

*Procaine Salicylate.*—The same procedure may be used, taking equimolecular quantities of Procaine base and salicylic acid. In this case an oily product is formed which, however, crystallizes slowly upon standing; m. p. 83° C.

A second method, used for these latter compounds and probably more adaptable to larger scale manufacture, is to fuse the two ingredients together on the water bath. The mass melts readily, then suddenly hardens as the salt is formed. This may then be powdered, washed with ether to remove any excess of either unreacted constituent and, if desired, recrystallized from water.

For purposes of spectrophotometric examination of these salicylates the same conditions and technique were employed. The transmission curves of Benzocaine, Butyn and Larocaine salicylates (Fig. 5) are almost identical with those of the respective bases, with perhaps a slight sharpening of the filter effect denoted by a small shift of the subsidiary bands to the right. All substances show good filtering effect in the band 290 to 310 mμ.

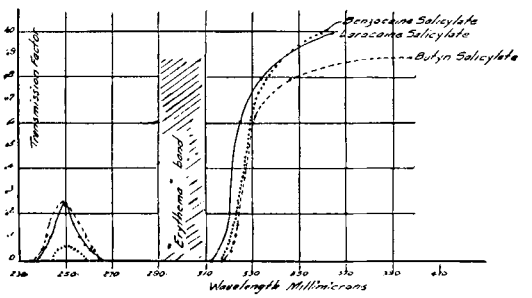



Fig. 5.—Transmission Spectra.
0.01% in ethanol. $d$ = 1 cm.

By way of further investigation the acetylsalicylic and salicylsalicylic salts of Larocaine base were made and examined. The former, made by both the above-described methods, was a glass-like mass which did not crystallize in the refrigerator. The latter was a crystalline solid, m. p. 131.9° C., soluble in boiling water and alcohol, slightly soluble in ether. Transmission curves of these together with Larocaine salicylate are shown in Fig. 6.

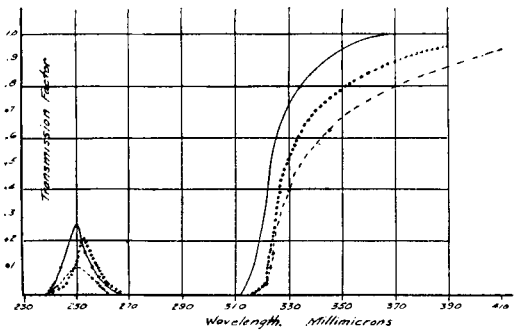



Fig. 6.—Transmission Spectra.
Larocaine salicylate ——. Larocaine salicyl salicylate ..... Larocaine acetyl salicylate --------. 0.01% in ethanol. $d$ = 1 cm.

From the foregoing it may be inferred that any of the local anesthetics derived from *p*-aminobenzoic acid might offer possibilities as sunscreens or filters for the wave band generally recognized as being the main cause of the severe erythema and pain resulting from sunburn. Spectrophotometric evidence is not necessarily a guarantee of efficacy under practical conditions so that the results observed may be taken only as indications of such potentialities. However, in these investigations actual trials were made of two compounds, both of which proved highly satisfactory. On the assumption that the thickness of the layer of any medicament or preparation applied to the skin by an individual may vary within extremely wide limits, it was considered advisable to use a much greater concentration of "filter" substance than appeared necessary by the spectrophotometer findings.

Prior to actual tests as a sunscreen, some preliminary pharmacological data were obtained with a view to discovering any irritant or other undesirable effects. One per cent aqueous solutions of Larocaine salicylate were applied to shaved areas of a rabbit's back without subsequent signs of irritation. After five days' remission the solution was again applied every fifteen minutes for three and one-half hours without obvious effect. Repeated applications to the arms, neck, face and hands of sundry individuals were made, allowed to dry and remain for several hours with similar negative results. In the outdoor tests a lotion and an aquaphilic type cream containing 1% of Larocaine salicylate were prepared and distributed to about 200 individuals, fully 90% of whom reported favorable results.

It would therefore seem from these observations that certain anesthetic ointments advertised to the public as remedies for sunburn pain may actually be efficient filters of the erythema-producing rays if the medicament used belongs to the class discussed. In these experiments only 1% of Larocaine salicylate was used, corresponding to about 0.75% of the standard available substance (hydrochloride) or to about 0.67% of base. Thus, in this low concentration it would seem unlikely that any great degree of surface anesthesia would be attained in cases of inadvertent burn. However, with increase of active substance the combination of protection from, and alleviation of, potential pain in extreme cases appears very desirable. This problem may be somewhat more complicated than it would first appear in view of the work of Regnier, *et al.*, (2) who showed that the anesthetic effect of many compounds of this series varied very considerably according to the nature of the combined acid. In the case of cocaine, for example, the salicylate showed four times the anesthetic activity of the hydrochloride when applied to the corneas of rabbits.

Use of the salicylate in preference to the base provides a sufficiently water-soluble compound to enable the use of aqueous media in formulating a "sunburn" preparation. The quantity required for normally adequate protection, at least in the case of Larocaine salicylate, is quite low—many commercially available substances used for similar purposes employing 5%, 10%, or even more of active material—so that the possibility of skin irritation from

the salicylic radical may scarcely be considered a serious objection.

SUMMARY

Alcoholic solutions of local anesthetic bases derived from *p*-aminobenzoic acid show strong absorption of ultraviolet light in the wave-length band 2700 to 3200 Å.

The somewhat water-soluble salicylates show similar phenomena with slightly improved "filter" characteristics. Acetylsalicylic and salicylsalicylic salts showed no obvious advantages over the salicylates.

One per cent aqueous preparations of Larocaine salicylate gave good results in actual trials as "sunscreens" and it is concluded that most surface anesthetics of this type offer interesting possibilities in the formulation of such preparations.

REFERENCES

(1) Marchlewski, L., and Mayer, J., *Bull. intern. acad. polon. sci.* (1929), p. 170.

(2) Regnier, J., Delange, R., and David, R., *J. pharm. chim.* (Paris), 23 (1936), 494.

Regnier, J., Brit. Pat. 477,882, 477,822; French Pat. 789,156.

Regnier, J., and David, R., *J. pharm. chim.*, 22 (1935), 16.

Regnier, J., and Quevauviller, A., *Compt. rend. soc. biol.*, 122 (1936), 251.

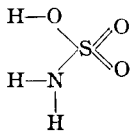
Regnier, J., Delange, R., and David, R., *Ibid.*, 202 (1936), 591.

# Quinine Sulfamate*

*By Kenneth H. Stahl† and R. A. Kuever‡*

Sulfamic acid is gaining prominence in the fields of technical, industrial, medical and pharmaceutical chemistry (1). Its salts possess some advantages over the corresponding salts of the mineral acids.

The structure and properties of sulfamic acid are given by Butler, Smith and Audrieth (2) and Cupery (3). Empirically, it is $HNH_2SO_3$, and is made commercially by the reaction of urea and fuming sulfuric acid. Its graphic formula is:



Dry sulfamic acid is a stable, nonhygroscopic, crystalline product. It is moderately soluble in water and formamide, slightly soluble in ethanol, acetone and ether. It is insoluble in hydrocarbons, chlorinated hydrocarbons, carbon disulfide and sulfur dioxide.

The solubility of sulfamic acid in water is decreased by the presence of sulfuric acid or sodium sulfate. It is practically insoluble in 70% to 100% sulfuric acid.

When dissolved in water, sulfamic acid is highly ionized. The solutions are strongly acidic, and show high conductivity.

It is practically stable in water solutions at ordinary temperature. At elevated temperatures it is slowly hydrolyzed to ammonium acid sulfate.

Salts of sulfamic acid are stable in neutral or alkaline solutions, which may be evaporated on the steam bath without hydrolysis of the amide group. All of the known salts of sulfamic acid, with the exception of a basic mercury salt, are soluble in water.

With the properties of sulfamic acid in mind, two quinine sulfamates were prepared. These are quinine sulfamate and quinine bisulfamate. A study was made of the physical properties, solubilities in various solvents, molecular formula and crystalline structure. Some interesting properties were revealed, particularly with regard to solubilities in water and alcohol.

EXPERIMENTAL

Quinine sulfamate was prepared from equimolecular quantities of quinine and sulfamic acid: 378 Gm. of quinine was dissolved in 500 cc. of alco-

* Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

† Abstract from a thesis presented to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the degree of Master of Science.

‡ Professor, College of Pharmacy, State University of Iowa, Iowa City, Iowa.