Infrared Absorption Ratio Method for Determination of Triethanolamine Salicylate in Ointment

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A rapid and convenient infrared method was developed for the assay of triethanolamine salicylate in an ointment base. The method involves drying the ointment, scanning the infrared spectrum from 5.5 to 8.7 μ, and calculating the ratio of the absorption peaks at 6.3 and 6.85 μ. Advantages of the method are that no chemical isolation or treatment of the drug is necessary and no weight or volume measurement of sample is required.

A METHOD was sought for determining triethanolamine salicylate (TEAS) salt complex (2, 2′, 2″-nitrilotriethanol salicylate) in ointment. A literature search turned up only three direct references to the compound (1–3); its analytical determination was not mentioned. It was desirable to have a method specific for the TEAS complex and not dependent on an analytical reaction of any of its components. Preliminary studies on colorimetric and titrimetric methods did not give promising results. Investigation of the infrared spectra of the complex and of the ointment base revealed that absorption by the ionized carboxyl group along with the absorption of the methylene groups in the system could be used as the basis for an assay method. Like most ointment bases, the one used in this work consists largely of high molecular weight aliphatic compounds, so the strongest absorption is due to methylene groups. Since the $pKa^{25°}$ for salicylic acid is 3.00, the contribution to the quantity of ionized carboxyl from any free salicylic acid present would be negligible. Hence the absorption by the ionized carboxyl group of the salicylic acid moiety of the TEAS complex is taken as specific for the TEAS content; the absorption peak occurs at about 6.3 μ in this system. (Commercial grades of triethanolamine contain varying amounts of diethanolamine with traces of monoethanolamine. Any salicylate complexes involving these amines would also contribute to this absorption band.) The CH_2 group absorbs at about 6.85 μ in this ointment system. The ester absorption band appears at about 5.8 μ. Under normal conditions (*i.e.*, temperatures less than about 65°), only a negligible amount, if any, of the ester would be present. At any rate, the ester would not contribute to the absorption at 6.3 μ by the ionized carboxyl of the TEAS salt; hence, this latter absorption would indicate correctly the content of salicylate complex.

Since the ratio of TEAS to CH_2 groups will always be the same in a given ointment sample or batch (assuming homogeneity) regardless of the quantity of ointment taken, the ratio of the absorbances of these two chemical entities is a measure of the relative amount of TEAS present. This eliminates the need for weight, volume, or thickness measurements of sample taken. For the assaying of ointments, this is a very desirable feature. The ratio of interest is the ratio of the absorbance at 6.3 μ to the absorbance at 6.85 μ.

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EXPERIMENTAL

Apparatus.—An infrared recording spectrophotometer with NaCl optics, two or three NaCl plates and holders or a demountable cell, an infrared heating lamp, a Wig-L-Bug (or similar vibrator-mixer) and stainless steel capsule and pellet, and a thermometer, microspatula, ringstand, and microscope slide were employed.

Preparation of Standard Curve.—A series of synthetic ointments was prepared containing these percentages of TEAS in ointment base (w/w): 5, 7, 8, 9, 9.5, 10, 10.5, 11, 12, 13, 15. Samples of these standards were prepared as outlined under *Procedure*, and the infrared spectrum of each was obtained from 5.5 to 8.7 μ on a Beckman IR 5 spectrophotometer. The absorbance ratio was calculated, and the plot of absorbance ratio *versus* per cent TEAS followed Beer's law over the region of interest.

Procedure.—Attach the heating lamp to a ringstand so that the lens is about 1 ft. above the base of the stand. Arrange a thermometer horizontally, so that it registers the temperature at the base; turn on the lamp and allow the temperature to reach about 60° before drying the sample. The temperature should not be allowed to rise above about 70°.

Mix the ointment thoroughly; with a microspatula, spread a layer of sample about $^1/_{16}$ in. or less in thickness on a glass slide. Place the slide directly under the lamp and next to the thermometer bulb. Note the time and temperature at the beginning and end of the heating period, which should be 10 minutes for an ointment containing about 60% water. Remove the slide from the heat and mix the melted sample with the spatula; when it has solidified after 1 minute or 2, scrape off the sample as much as possible into the stainless steel capsule with the pellet and vibrate it in the Wig-L-Bug for 20 seconds. This assures thorough mixing of the crystals of TEAS with the dehydrated ointment base, which is essential for obtaining an accurate assay result.

Prepare two NaCl salt plates as windows, warming them slightly under the lamp. Apply a thin film of the dried mixed ointment to the larger plate, then press a smaller plate over it to form a continuous film of an area appropriate to the cross section of the sample beam of the spectrophotometer. Adjust the sample thickness so that the absorbance at 6.85 μ is approximately 0.53 (or 30% T) and obtain the infrared spectrum from 5.5 to 8.7 μ. It is desirable to reduce the background absorption by placing a single salt plate in the reference beam.

Draw a base line joining the transmission maxima at 5.6 and 8.55 μ. Determine the appropriate absorbance values and calculate the 6.3/6.85 ratio from

$$\text{ratio} = \frac{(A_{6.3}{}^{p}) - (A_{6.3}{}^{bl})}{(A_{6.85}{}^{p}) - (A_{6.85}{}^{bl})}$$

where

$A_{6.3}{}^{p}$, $_{6.85}$ = absorbance of peak at 6.3 or 6.85 μ

$A_{6.3}{}^{bl}$, $_{6.85}$ = absorbance of base line at 6.3 or 6.85 μ

DISCUSSION

It is important in the sample treatment to ascertain that all water is driven out. There are water absorption bands in the region of interest, and the presence of water in the sample being scanned will give variable results for the absorbance ratio. On the other hand, care must be taken that the temperature does not rise high enough to cause ester formation, which would obviously result in a lowered salicylate salt content. There should be no problem if the procedure outlined above is followed. Other drying methods are available, but this was the method of choice in terms of convenience and simplicity.

Replicates of four spectra for each of 10 lots of ointment gave an average deviation of ± 0.006 in the absorbance ratio, which represents an error of approximately 0.2% in TEAS content. This precision is adequate for routine control of commercial samples.

The time required for the assay is about 30 minutes and includes drying and preparing the sample, running four spectra, and calculating results.

SUMMARY

A convenient, rapid, and accurate absorbance ratio method for the assay of triethanolamine salicylate in ointment base is proposed. The method is based on the spectrophotometric measurement of the infrared absorption of the salicylate ionized carboxyl and the system methylene groups. No measurement of amount of sample taken is necessary, and no standard needs to be run after the standard curve has been established.

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Mannich Bases and Alcohols from Hexamethylenimine

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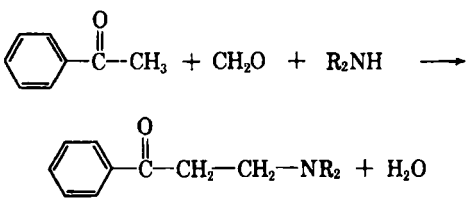
The synthesis of a group of Mannich bases and secondary and tertiary γ-aminoalcohols derived from hexamethylenimine are described. These compounds are to be screened for possible pharmacological action.

THE MANNICH reaction has been extensively reviewed (1–4) and consists of the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride salt, an aldehyde, and a compound capable of supplying one or more replaceable hydrogen atoms. A typical condensation with acetophenone as the active hydrogen compound may be illustrated as



The mechanism of the Mannich reaction has been investigated by others (5–9). Hellmann and Opitz (5) and Cummings and Shelton (6) proposed that the reaction is initiated by a condensation between the amine and formaldehyde to yield an aminomethanol. The subsequent steps may be visualized as follows: attack of a proton on the oxygen atom of the aminomethanol, followed by expulsion of water, leads to the formation of a resonance-stabilized carbonium-immonium ion. This carbonium ion then reacts with the carbanion, which results from ionization of the active hydrogen-containing compound.

A large number of β-aminoketones (Mannich bases) have been prepared and tested as antispasmodics, local anesthetics, analgesics, and antibacterial agents (10–18). Secondary γ-aminoalcohols, prepared from Mannich bases by reduction with sodium borohydride (15, 19, 20), and tertiary γ-aminoalcohols, obtained by reacting Grignard reagents with Mannich bases (21), have been prepared and tested for similar pharmacological activity (15, 22, 23).

Reduction of piperidine Mannich bases to yield the corresponding secondary alcohols or reaction with Grignard reagents to yield the appropriate tertiary alcohols gave agents of greater antispasmodic activity (10, 22). Mannich bases derived from propiophenone appear to have enhanced analgesic activity (16, 21) and are better local anesthetics (12, 13) and antifungal agents (16) than acetophenone derivatives. Certain β-aminoketones with complex amine moieties have shown an unexpected order of antibacterial activity (24).

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