

New Infrared Technique for the Determination of Impurity in Substituted Anthranilic Acid: Effect of *Ortho* Substitution on the Aromatic Acid Carbonyl Band

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Abstract □ A new IR technique has been developed for the determination of halogenated impurity in substituted anthranilic acid. The method is applicable for the quantitative determination of small amounts of those compounds containing carbonyl groups whose electronic structures are affected by substitution groups. The relationship between the displacement of the carbonyl band frequency due to the presence of the electron-withdrawing or -donating groups and the effect of hydrogen bonding, is explained and the usefulness of the proposed method is discussed.

Keyphrases □ Anthranilic acid, substituted—impurity determination □ Acetonitrile, solvent—anthranilic acid □ IR spectrophotometry—analysis

Preliminary investigation of an interesting type of substituted anthranilic acids (I)¹ using TLC methods generally showed a content of 1–3% halogenated impurity (II). As TLC could not be used for accurate quantitative determination of this impurity, an attempt was made to develop a suitable analytical method capable of differentiating the impurity from the parent compound.

Since the spectra of the impurity, the parent compound, and therefore a mixture of the two, were essentially identical, UV methods proved inadequate. However, a comparison of the mineral oil mull spectra of material known to contain the halogenated impurity with that of specially prepared pure I, showed an additional shoulder in the carbonyl region. A review of the respective I and II spectra indicated that the shoulder was specific to the halogenated impurity (Fig. 1, A and B).

Although IR spectroscopy can be employed with particular success in the functional group region of the spectrum where the inductive and resonance effects of many groups alter the frequency and the intensity of the stretching absorption band, quantitative determination of a small amount of impurity is precluded when the absorption due to the impurity appears only as a shoulder. In many such cases, the use of the so-called “differential method” (1) resolves the situation. The results of this method, however, are only valid when the frequency of the analyzed band is independent of concentration changes of the impurity. The differential technique could not be employed in the present study since the proximity of the respective acid carbonyl bands caused a shift in frequency with concentration changes. Therefore, a procedure was developed in which the amount of halogenated impurity was increased by known amounts and the once insignificant shoulder was successfully resolved to an independent

measurable band without changing the frequency of absorption.

EXPERIMENTAL

Apparatus and Reagent—A recording spectrophotometer² equipped with 1-mm. sodium chloride cells was used to record the spectra; acetonitrile spectrograde was the solvent.

Preparation of Stock Solution—A solution containing 0.2% II in acetonitrile was prepared.

Preparation of Standard Solution—To exactly 90, 86, and 82 mg. of Standard I in separate 10-ml. volumetric flasks, 5, 7, and 9 ml., respectively, of II stock solution were pipeted and the contents were diluted to volume with acetonitrile.

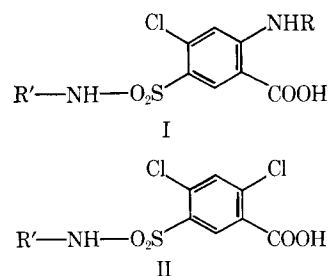
Preparation of Sample Solution—To 90 and 88 mg. of sample in separate 10-ml. volumetric flasks, 5 and 6 ml., respectively, of stock solution were pipeted and the contents were diluted to volume with acetonitrile.

Procedure—The standard and sample solutions were transferred in turn to a 1-mm. sodium chloride cell and the spectrum was scanned from 1,900 to 1,650 cm^{-1} with acetonitrile as a blank in the reference cell using a suitable IR spectrophotometer.

Since the regular base-line technique cannot be applied for the calculation because of the steep slope, the following modified technique is used: a line drawn tangent to the curve between 1,900 and 1,850 cm^{-1} is extended to 1,600 cm^{-1} . The transmittance value at the intercept of this line with a vertical line drawn to the peak maximum at about 1,737 cm^{-1} , is taken as I_0 . The transmittance reading at about 1,737 cm^{-1} is taken as I. The absorbances ($A = \log I_0/I$) of the standard solution are plotted against the weight of II added to obtain the calibration curve. The absorbances of the sample solutions are determined in a similar manner.

DISCUSSION

The two types of compounds considered in this study have the following structural formulas (I, main; II, impurity)



R and R' are substitutions in the chemical structure which have no significant spectral influence on the proposed method.

Particular solubility problems were encountered in this case in addition to the general problem of limited sensitivity in IR procedures for the quantitative determination of small amounts of contamination. Insufficient solubility was found in solvents such as chloroform and carbon tetrachloride and otherwise suitable solvents such as carbon disulfide and dioxane, were not transparent in the region of interest. Acetonitrile, among all the solvents tested, was

¹ See structural formulas under *Discussion*.

² Perkin Elmer IR 621.

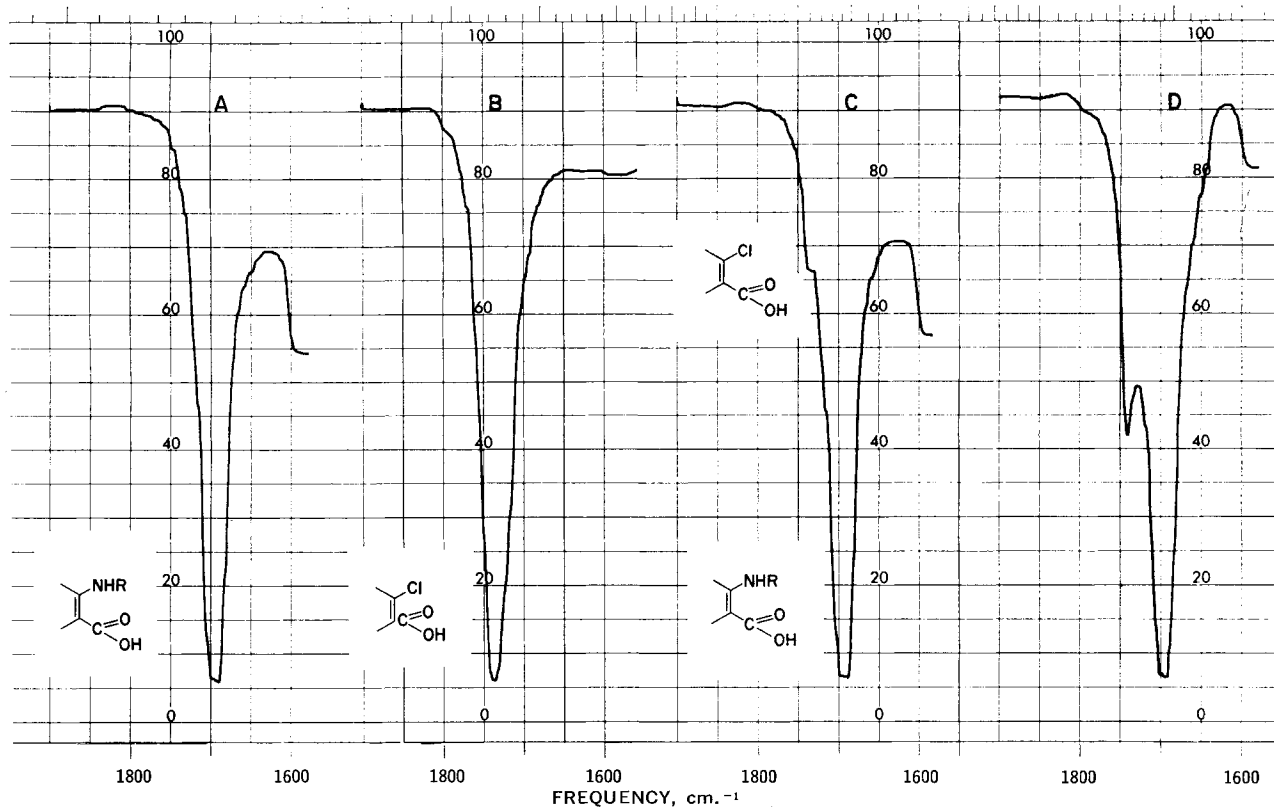


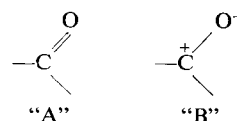
Figure 1—IR absorption spectrum of A, I (pure substance); B, II (halogenated impurity); C, typical production batch; D, production batch with 10% added impurity.

the only one satisfactory with respect to both solubility and transparency.

In an acetonitrile solution of I, the carbonyl band appears at about $1,690\text{--}1,700\text{ cm}^{-1}$; whereas, the carbonyl band of II appears in the $1,735\text{--}1,745\text{ cm}^{-1}$ region. The presence of II as an impurity in I manifests itself as a shoulder at $1,737\text{ cm}^{-1}$ when just a few percent is present, and a measurable peak for a content of about 8% or more (Fig. 1, C and D). Therefore, to a sample containing an unknown amount of impurity, specific amounts of II are added to bring the absorbance of the peak at $1,737\text{ cm}^{-1}$ (of 1% acetonitrile solution) to an easily measurable point. The total absorbance of the impurity is then calculated and evaluated with the aid of a standard calibration curve. The linear calibration curve is obtained using the calculated absorbance values for a specially prepared pure sample of I to which known amounts of II are added. The amount of II originally present in the unknown sample of I is found by subtracting the amount of II added from the total amount of impurity found as calculated from the standard calibration curve. The standard calibration curve was consistently reproducible throughout the entire study (see Table I).

One notes the $40\text{--}50\text{-cm}^{-1}$ separation in the frequency of carbonyl band absorption for I and II (Fig. 1, A and B) which provides the foundation for the proposed method of analysis. As the respective groups *ortho* to the acid carbonyl are the only points of difference between the two similar molecules, it is evident that the displacement is due to the effect they assert. The existence of internal hydrogen bonding due to the linkage between the *o*-amine and

carbonyl groups, in the case of the substituted anthranilic acid, which considerably lowers the normal frequency of the acid carbonyl band, has been widely cited in the literature (2, 3). The further effect of the respective electron-withdrawing and -donating groups can be explained by the resonance form of the acid carbonyl group as shown below:



As can be seen from the electronic structure of the carbonyl group, electron-donating groups such as amines will stabilize "B," decrease the force constant, and thus lower the absorption frequency. Furthermore, the presence of electron-donating groups increases

Table II—Substitution Effect on Frequency of Acid Carbonyl Band

Compound	Frequency, cm^{-1}
	1,720–1,737
	1,718–1,742
	1,685–1,700
	1,688–1,693

Table I—Reproducibility of Standard Absorbance Values

Impurity Added, mg.	Absorbance ^a	Mean Deviation
10	0.217	± 0.001
12	0.247	± 0.002
14	0.277	± 0.005
16	0.310	± 0.002

^a Average of five determinations.

Table III—Determination of Impurity in Commercial Samples

Production Sample	Impurity Found, % ^a	Mean Deviation, %
A	3.60	±0.04
B	3.54	±0.02
C	1.76	±0.06
D	0.71	±0.07

^a Average of triplicate assays.

the dipole moment, creating a more intensive absorption band due to the greater vibration. Electron-withdrawing groups such as halogens have the opposite effect. Table II lists the respective frequencies of acid carbonyl band absorption of 1% acetonitrile solutions of compounds with electron-withdrawing and electron-donating substitution *ortho* to the carboxylic acid group. These data indicate that both the presence of intramolecular hydrogen bonding and whether *ortho* substitution is electron-withdrawing or -donating, contribute to a 40–50-cm.⁻¹ frequency difference. Such differences in frequency make impurity determinations by the proposed method possible. Furthermore, it was observed that electron-donating and -withdrawing substitution *meta* to the carbonyl groups has minimal or no effect on the carbonyl band displacement.

The proposed method can be applied successfully to those samples where the contamination is 1% or greater (see Table III). Below

this amount the accuracy of the method is limited; however, results obtained in such cases have shown agreement with those estimated by collaborative methods such as TLC and GLC.

SUMMARY

A new technique in the field of IR spectroscopy has been developed which offers the possibility of quantitative analysis of very weak absorption bands appearing as shoulders. These shoulders may often be resolved to measurable bands permitting accurate evaluations to be made in cases where previously reported techniques fail to work.

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Synthesis of Certain *N*¹- and *N*⁴-(5-Nitro-2-pyridyl)-Substituted Sulfonamides

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Abstract □ The condensation of 2-chloro-5-nitropyridine with a number of sulfonamides is described. Sulfadiazine, sulfamerazine, sulfathiazole, sulfapyridine, sulfisoxazole, sulfamethoxy-pyridazine, and sulfadimethoxine afforded the *N*⁴ derivatives *via* the application of Banks' procedure. 4-Homosulfanilamide using Ullmann's and Mangini's conditions, yielded the *N*¹ and *N*⁴ derivatives, respectively. With benzylsulfonamide and benzenesulfonamide adopting Ullmann's method the corresponding *N*-substituted derivatives were obtained.

Keyphrases □ Sulfonamides, *N*¹, *N*⁴-(5-nitro-2-pyridyl)-substituted —synthesis □ Condensation reaction—sulfonamide derivative synthesis

In two earlier publications (1, 2) the authors reported the condensation of 2-chloro-5-nitropyridine with different amino compounds including sulfaguanidine as a representative of the group of sulfonamides. In continuation, other sulfonamides were condensed with the same halonitroheterocycle, in the hope that the introduction of the 5-nitro-2-pyridyl moiety might enhance the antimicrobial activity of the parent compounds (3–7).

2-Chloro-5-nitropyridine was prepared from 2-aminopyridine according to a method described earlier

(1). Of the sulfonamides: 4-homosulfanilamide and benzylsulfonamide were synthesized adopting reported procedures. The former compound was prepared from benzylamine by acetylation (8–11), chlorosulfonation, amidation of the sulfonyl chloride, subsequent hydrolysis of the acetyl amino group, and finally isolating the product as the hydrochloride (12, 13). Benzyl sulfonamide was obtained from benzyl chloride by treatment with sodium sulfite, converting the sulfonate thus obtained to the acid chloride using phosphorus pentachloride and finally to the amide by mixing with excess concentrated ammonia (14).

Several attempts were made to condense 2-chloro-5-nitropyridine with the *N*¹-substituted sulfonamides. Bobranski's method (15, 16) did not give satisfactory results while Ullmann's conditions (17–19) were unsuccessful. Likewise, the use of solvents such as pyridine (20), pyridine-ethanol, dioxan, and ethylene glycol (in presence and absence of potassium carbonate) did not improve matters. Nevertheless, the condensation was successfully achieved by conducting it in aqueous hydrochloric acid in presence of varying amounts of ethanol (to enhance solubility and decrease volatility of 2-chloro-5-nitropyridine) following Banks' directions