IR Determination of Trace Quantities of Dicyandiamide and Cyanamide in Guanidine Sulfate

TIBOR URBANYI and ARMIN WALTER*

Abstract □ A sensitive quantitative IR absorption method was developed for the determination of dicyandiamide as an impurity in a pharmaceutical preparation. This method is suitable for the determination of dicyandiamide in very low concentrations in insoluble guanidines and for the quantitative detection of dicyandiamide in many other compounds. The method is based on the determination of the nitrile stretching vibration in the region of 2200 cm.$^{-1}$. Although dicyandiamide forms as a by-product in an alkaline solution from the excess of cyanamide used in the reaction, the proposed method utilizes the separation of cyanamide and dicyandiamide by a simple extraction procedure, using methylene chloride and 2-ethoxyethanol as solvents. The sensitivity of the method was improved by using an internal standard technique. The superiority of this method over existing methods is discussed, along with the importance and usefulness of IR absorption, particularly in everyday pharmaceutical analysis.

Keyphrases □ Dicyandiamide—separation, IR analysis, particularly in guanidine sulfate □ Cyanamide—separation, IR analysis, particularly in guanidine sulfate □ Guanidine sulfate—separation, analysis of dicyandiamide and cyanamide □ IR spectrophotometry—analysis, trace dicyandiamide and cyanamide

Cyanamide, although a classical raw material for organic synthesis (1), was formerly prepared either in small quantity in a laboratory (2) or in commercial quantity for captive use. Its tendency to react with itself, predominantly to form dimers, was a barrier to commercial development until recently. Efforts to circumvent this tendency have succeeded, and the stabilized anhydrous monomer (3) and a concentrated aqueous solution have become available commercially. Tonnage agricultural and metallurgical applications have been described (4).

In the pharmaceutical industry, cyanamide is particularly useful in the synthesis of guanidine derivatives (5), but dimerization should be eliminated or, if unavoidable, minimized. In either case, analytical controls to assure drug purity are needed.

On reviewing the literature data of the determination of dicyandiamide and cyanamide, it was found that the methods can be classified into several categories: titrimetric, polarographic, colorimetric, gravimetric, and chromatographic.

To the authors' knowledge, only two IR spectrophotometric (6, 7) dicyandiamide determination procedures are reported in the literature. The measurement of the absorption in the nitrile region is based on the utilization of an internal standard in paraffin oil or in a KBr pellet. The authors claim that the method is fairly sensitive, but the particle size of the sample, especially in oil, must be critically controlled. Titrimetric procedures are commonly used for the quantitative determination of dicyandiamide (8) as well as for cyanamide (9). However, reducing agents and aminoguanidine should be removed before the silver nitrate titration. The authors pointed out that the speed of operation is critical. The polarographic method (10) for the determination of dicyandiamide is complicated and time consuming. Colorimetric methods (11) are based on the reaction with pentacyanoammoniumferrate, which yields a red complex with cyanamides. Gravimetric determinations are often used (12, 13); dicyandiamide is hydrolyzed and allowed to react with picric acid to form guanylurea picrate. This method suffers from the typical experimental problems that arise with the gravimetric technique. Chromatographic methods were reported which deal with the separation and detection of cyanamide and its derivatives (14, 15). However, both papers only gave data for the quantitative determination of urea and not for cyanamide and dicyandiamide. Quantitatively, as many as 16 cyanamide derivatives may be separated by this technique.

Since the industrial application of cyanamide has grown rapidly, it was obvious that a suitable analytical method was needed for its determination. It was found that unreacted cyanamide undergoes dimerization to dicyandiamide if the reaction mixture is slightly alkaline. However, in a process where the reaction mixture is neutral or slightly acidic, dimerization does not occur and cyanamide remains as an impurity.

This paper describes an IR absorption method which can be used routinely, primarily for the quantitative determination of dicyandiamide. Cyanamide, another possible impurity, can be determined in the parent compound with an additional extraction. The method is based on the measurement of the C≡N stretching vibration in the region of 2200 cm.$^{-1}$.

EXPERIMENTAL

A recording spectrophotometer[1], equipped with 0.1-mm. sodium chloride cells, was used to record the spectra. Methylene chloride and 2-ethoxyethanol[2] were the solvents.

Preparation of Stock Solutions—Solutions containing 1 mg./ml. cyanamide in methylene chloride and dicyandiamide in 2-ethoxyethanol were prepared.

Preparation of Standard Solutions—Pipet 4, 6, 8, and 10 ml. of stock solutions into separate 10-ml. volumetric flasks, and dilute to volume with the appropriate solvents.

Preparation of Sample Solutions—Accurately weigh 1 g. of sample (guanidine compound) into a centrifuge tube, and extract several times with a small portion of methylene chloride. Transfer the solution onto a sintered-glass funnel, and filter it into a 10-ml. volumetric flask. This solution is for the cyanamide assay. Extract the remaining dry powder further with several small portions of 2-ethoxyethanol, and collect the filtrate in another 10-ml. volumetric flask. This solution is for the determination of dicyandiamide.

[1] Perkin-Elmer IR 621.
[2] Cellosolve.

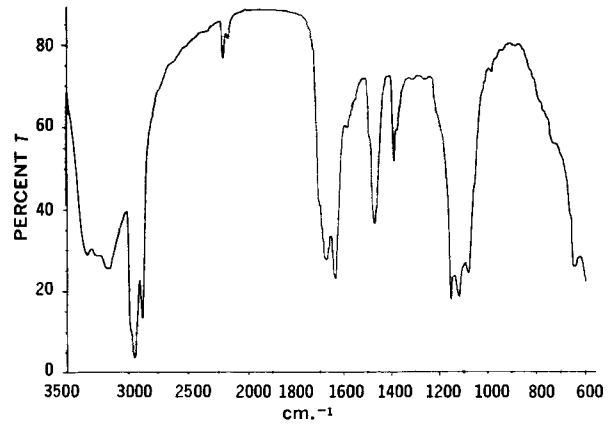

Figure 1—*IR absorption spectrum of the crude guanidine sulfate in a mineral oil mull.*

Procedure—Transfer the standard and sample solutions in turn to 0.1-mm. sodium chloride cells, and place the solutions into the spectrophotometer. To obtain reliable absorption values, the instrument is set at 3× ordinate scale and the speed, attenuation, and slit program are adjusted according to the instrument manual specification. The instrument is set to scan from 2550 to 2000 cm.$^{-1}$, using the appropriate solvents as blanks in the reference cell. By using the regular baseline technique, the absorbances at the maxima are calculated. The absorbance values of the standard solutions are plotted against the weight of the standards to obtain the calibration curve. The amount of impurities in the sample solutions is determined from the calibration curve in a similar manner.

The absorption caused by the stretching vibration of the triple bond of nitriles occurs at 2250 cm.$^{-1}$ for cyanamide and 2200 cm.$^{-1}$ for the dicyandiamide.

DISCUSSION

The IR absorption technique is seldom used for the quantitative determination of small amounts of impurities because of the lack of sensitivity. This technique is superior to other methods because of its specificity, but it can be applied only for quantitative determination of compounds that have strongly absorbing vibration groups. Cyanamide and dicyandiamide, the latter being the more probable contaminant, have a fairly strong absorption in a selective region which can be considered for quantitative determination.

Because the solubilities of cyanamide and dicyandiamide are quite different, the selection of proper transparent solvents for their separation was critical. Polar solvents were not transparent in the region of interest; they also dissolved the parent compound, which was undesirable because of potential interference. Nonpolar solvents are transparent in the region of interest, but the solubility of both cyanamide and dicyandiamide is negligible. Methylene chloride was found to be a suitable solvent for cyanamide because dicyandiamide

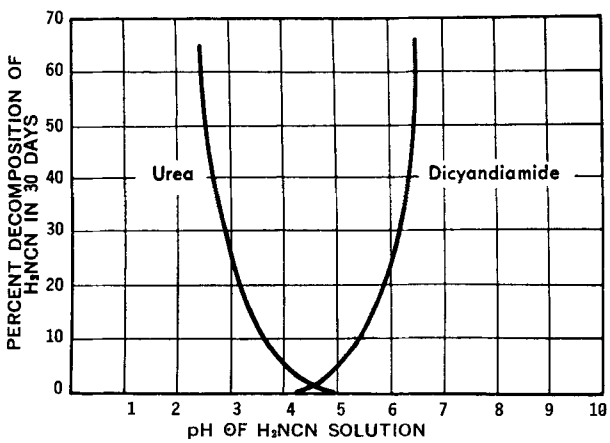

Figure 2—*Stability of cyanamide in aqueous solution.*

Table I—Reproducibility of Standard Absorbance Values

Percent Concentration	Cyanamide: Average[a] Absorbance	Cyanamide: Percent Standard Deviation	Dicyandiamide: Average[a] Absorbance	Dicyandiamide: Percent Standard Deviation
0.04	0.0510	0.62	0.0347	0.64
0.06	0.0785	0.65	0.0524	0.95
0.08	0.1027	1.32	0.0706	0.79
0.10	0.1278	0.54	0.0876	0.79

[a] Average of five determinations.

was completely insoluble and the solubility of the guanethidine compound was negligible. 2-Ethoxyethanol was found to be a suitable solvent for dicyandiamide, and the product had a low solubility. Although the cyanamide and dicyandiamide were both soluble in 2-ethoxyethanol, their separate determinations in a single solvent were impossible because of spectral interferences due to close absorption.

The IR spectrum in a mineral oil mull of the crude guanidine sulfate containing dicyandiamide as an impurity can be seen in Fig. 1. The weak absorption band observed at 2200 cm.$^{-1}$ is characteristic of the C≡N stretching frequency because of dicyandiamide remaining in the sample before recrystallization. The disappearance of this characteristic nitrile absorption band in a mineral oil mull after recrystallization is indicative of a higher quality compound; however, it does not mean that the impurity has been completely removed. The proposed method is sensitive enough to detect any remaining impurities which, in such cases, is below 0.5%.

The guanidine sulfate is basic enough to dimerize any cyanamide present to dicyandiamide. Although cyanamide is fairly stable in the solid state and in solution, in both cases it dimerizes rapidly to dicyandiamide in the presence of traces of alkali or heat. The stability of cyanamide in an aqueous solution can be seen in Fig. 2. To prove the dimerization of cyanamide, the following test was performed. A mole-to-mole portion of cyanamide dissolved in methylene chloride was mixed with basic guanidine sulfate, and the mixture was stirred overnight at room temperature. After the methylene chloride was completely removed, the solid sample was subjected first to methylene chloride and then to 2-ethoxyethanol extraction. The extraction with methylene chloride showed no evidence of the presence of cyanamide, while dicyandiamide was quantitatively recovered in the 2-ethoxyethanol extract. This test was controlled by TLC, and the absence of cyanamide and the presence of dicyandiamide were noted.

A similar test was carried out to demonstrate that the dimerization does not occur if the reaction mixture is neutral or slightly acidic. The guanidine monosulfate (molar base-to-acid ratio of 1:1) was mixed with a methylene chloride solution of cyanamide. The mixture was treated as before, and finally the dry powder was subjected to methylene chloride and 2-ethoxyethanol extraction. As expected, only the unchanged cyanamide was recovered. Tests were performed to exclude the possible formation of an impurity from the starting material and dicyandiamide. These experiments indicated that no interaction occurred between the two compounds under reaction conditions similar to those used in the process.

Table II—Separation of Cyanamide and Dicyandiamide by Extraction Procedure

	Cyanamide[a]	Dicyandiamide[a]
Average absorbance	0.0515	0.0549
Percent standard deviation	0.91	1.07
Percent recovery	100.0	101.0

[a] Average of five determinations.

Table III—Recovery of Dicyandiamide in Synthetic Mixture

Average absorbance[a]	0.0393
Percent standard deviation	0.57
Percent recovery	101.5

[a] Average of three determinations.

Table IV—Determination of Dicyandiamide in Crude Sample

Sample	Percent Dicyandiamide[a]
A	0.10
B	0.48
C	0.30

[a] Average of duplicate determinations.

Linear calibration curves, which follow Beer's law, were obtained for cyanamide and dicyandiamide using the pure substances in the appropriate solvents. The reproducibility of the absorbance values with consecutive determinations can be seen in Table I. Experimental data, however, indicate that the standard calibration curves are reproducible and linear over a wide range. Table II summarizes the data obtained for a synthetic mixture of cyanamide and dicyandiamide (4:6). These data indicate that satisfactory separation was achieved for these components using the proposed extraction procedure. The recovery of dicyandiamide, the only contaminant resulting from the preparation of guanidine sulfate, was further investigated utilizing synthetic mixtures. To a dicyandiamide-free sample of guanidine sulfate, a known amount of dicyandiamide was added; after proper mixing, it was extracted with 2-ethoxyethanol. The results of the recovery of dicyandiamide can be seen in Table III for consecutive determinations.

Fairly accurate results were obtained when several crude samples were analyzed for dicyandiamide when the amount of contamination was over 0.2%. The results of these tests are summarized in Table IV. However, the results in Table V indicate that purified samples usually have less than 0.2% of dicyandiamide. In the latter case, detection of the dicyandiamide, or in special cases the cyanamide, can be appreciably improved with a simple technique (16), which offers significantly greater sensitivity than the more conventional techniques. This technique is based on the fact that upon addition of a known amount of the impurity to the sample, the absorption of the impurity can be significantly increased if the detection of very small amounts is desired. If the amount of impurity added is substracted from the total absorbance value, the net amount of impurity found in the sample results. Figure 3 illustrates the application of the modified technique. This technique was successfully applied for dicyandiamide detection in the guanidine sulfate where the concentration of this component was as low as 0.015%.

SUMMARY

IR absorption, as employed in this study, was found to be a suitable technique for the quantitative determination of dicyandiamide as an impurity in guanidine sulfate. The proposed method can be used for the separation of cyanamide from the dicyandiamide with a simple extraction procedure. Both compounds are considered to be moderately toxic; therefore, a sensitive method is required for their determination in pharmaceuticals. The method presented is superior to procedures reported in the literature because of its increased sensitivity and specificity. The limit of detection of the cyanamides was improved by a simple technique where the sensitivity of the detection is critical. The formation of dicyandiamide during the process is explained, and the accuracy of the method is discussed.

Table V—Determination of Dicyandiamide in Recrystallized Samples by Modified Technique

Sample	Dicyandiamide Added, mg.	Total[a] Dicyandiamide Found, mg.	Percent Impurity
A	5.0	5.25	0.025
B	5.0	5.00	0.000
C	5.0	5.25	0.025
D	5.0	5.15	0.015

[a] Average of duplicate determinations.

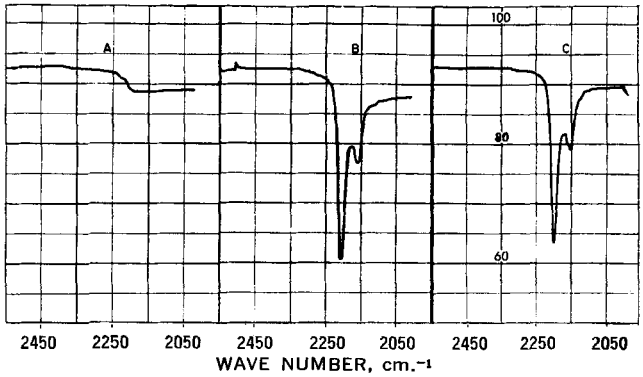

Figure 3—*IR absorption spectrum of: A, sample containing less than 0.1% dicyandiamide with regular method; B, same sample as in A with added 5.0 mg. dicyandiamide; and C, standard solution containing 5.0 mg. dicyandiamide.*

REFERENCES

(1) E. Erlenmeyer, *Ann. Chem. Pharm.*, **146,** 258(1868).
(2) L. A. Pinck and J. M. Salisbury, *Inorg. Syn.*, **3,** 39(1950).
(3) J. R. McAdam and F. C. Schaeffer, in "Encyclopedia of Chemical Technology," 2nd ed., vol. 6, A. Standen, Ed., Interscience, New York, N. Y., 1965, pp. 553–573.
(4) *Ibid.*, p. 559.
(5) U. S. pat. 2,928,829 (Mar. 15, 1960).
(6) K. Seiffarth, W. Wohlrabe, and H. W. Ardelt, *Z. Anal. Chem.*, **217,** 345(1966).
(7) B. I. Sukhorukov and A. I. Finkelshtein, *Invest. Akad. Nauk. SSSR*, **23,** 1230(1959).
(8). I. S. Novikova, S. A. Trofimova, *et al.*, *Lakokrasoch. Mater. Ikh Primen.*, **1967,** 70.
(9) M. G. Ivanov and V. G. Golov, *State Sci. Res. Design Inst. Nitrogen Ind. Prod. Org. Syn. Dzherzhinsk*, **32,** 289(1966).
(10) H. Woggon, V. Koehler, and O. Korn, *Deut. Akad. Wiss. Berlin Ernaehrungsforsch.*, **11,** 548(1966).
(11) V. Novak and H. Hruska, *Drajska Hyg. Epidemiol. Stanice, Ceske Budejovice*, **17,** 216(1967).
(12) O. T. Rotini and F. Navari, *Chim. Agro. Univ. C.N.R. Pisa*, **49,** 854(1967).
(13) F. Yamazoe and J. Imai, *Bunseki Kagaku*, **9,** 877(1960).
(14) J. E. Milks and R. H. Janes, *Anal. Chem.*, **28,** 846(1956).
(15) O. Korn and H. Woggen, *Akad. Wiss. Berlin*, **11,** 278(1964).
(16) T. Urbányi and S. Budavari, *J. Pharm. Sci.*, **58,** 905(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received December 17, 1970, from the *Analytical Research and Development Division, CIBA Pharmaceutical Co., Summit, NJ 07901*

Accepted for publication July 1, 1971.

The authors thank Gilmer T. Fitchett for his aid in preparing the compounds analyzed and for his advice. They also thank B. P. Korzun and his group for their assistance in interpreting the TLC data.

* Present address: CIBA Ltd., Basle, Switzerland.