The identification of a stable epoxide as a major metabolite of carbamazepine is of interest as a possible precursor of hydroxylated metabolites which are now being identified and may be present in the urines of subjects treated with carbamazepine.

Although the pharmacological properties of carbamazepine-10,11-epoxide are still unknown, it is tempting to speculate that this metabolite may be involved in the cases of agranulocytosis ascribed to the administration of carbamazepine (2).

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DRUG STANDARDS

Rapid Analysis of Iodochlorhydroxyquin and Related Halogenated 8-Hydroxyquinolines *via* GLC of Their Trimethylsilyl Ethers

M. P. GRUBER, R. W. KLEIN▲, M. E. FOXX, and J. CAMPISI

Abstract □ A rapid GLC analysis procedure of the trimethylsilyl ethers of 8-hydroxyquinoline and related halogenated 8-hydroxyquinolines, with significantly greater accuracy and precision than official procedures, is presented. A 5–20-fold increase in sensitivity is obtained, allowing detection, identification, and quantitation of impurities at low levels. The method is free of apparent interferences and may be extended to provide rapid, accurate analyses of diiodohydroxyquin and other halogenated 8-hydroxyquinolines.

Keyphrases □ Iodochlorhydroxyquin and related 8-hydroxyquinolines—rapid GLC analysis □ 8-Hydroxyquinolines, halogenated—rapid GLC analysis □ GLC—analysis, iodochlorhydroxyquin and related halogenated 8-hydroxyquinolines □ *N*-Trimethylsilylimidazole—silylating reagent for rapid GLC analysis of halogenated 8-hydroxyquinolines

The procedure employed in the USP XVIII (1) for the assay of iodochlorhydroxyquin marks a significant departure from that listed in an earlier edition (2), which employed an oxygen flask combustion followed by a potentiometric titration of the liberated halides. Iodochlorhydroxyquin in creams, ointments, and suppositories was measured spectrophotometrically in glacial acetic acid at 325 nm. Both procedures have given way to the IR technique of Urbanyi *et al.* (3), which involves the absorbance peak of 14.4 μ (694 cm.$^{-1}$) peculiar to iodochlorhydroxyquin among the halogenated 8-hydroxyquinolines.

Previous investigations with spectrophotometric, colorimetric, titrimetric, polarographic, and chromatographic procedures suffered from one common failing; each was unable to distinguish one or more impurities from one another or from the parent compound. The TLC method of Korzun *et al.* (4) provided the best separation of halogenated 8-hydroxyquinolines but failed to separate 5,7-dichloro-8-hydroxyquinoline,

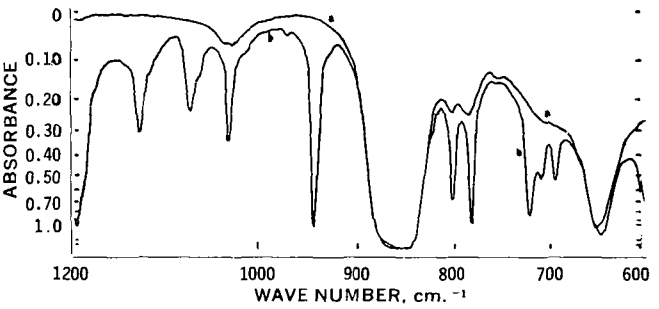

Figure 1—*IR spectrum of iodochlorohydroxyquin (5.00 mg./ml.) in carbon disulfide (b) superimposed on carbon disulfide (a) in 3-mm. sodium chloride cell.*

Table I—Minimum Detectable Limits of Impurities in Iodochlorhydroxyquin (0.5% w/v Sample) by IR

Compound	Minimum Detectable Limit, %[a]
5,7-Dichloro-8-hydroxyquinoline	2.9
5-Chloro-8-hydroxyquinoline	0.5
5,7-Diiodo-8-hydroxyquinoline	2.7

[a] Determined as the quantity required to record an absorbance of 0.010 at the wavelength measured.

which was present in many commercial samples of iodochlorhydroxyquin, and, by the authors' admission, was a semiquantitative rather than quantitative procedure.

Bigeard *et al.* (5) developed an IR method prior to Urbanyi *et al.* (3); it was based on the potassium bromide disk technique in the far IR region. The special instrumentation involved, combined with the usual difficulties associated with the potassium bromide technique, limited its applicability.

Although the modifications introduced by Urbanyi *et al.* (3) provide a more specific and accurate determination than any previously published instrumental procedure and is equivalent to the classic phase-solubility technique (6), it also suffers from several deficiencies. Absorptivities in the IR region are significantly lower than those obtainable in either the UV or visible range of the spectrum, with a resulting loss in precision and sensitivity. These difficulties may be partially overcome by the use of larger samples and/or increased path length. However, the former introduces the secondary consideration of solubility limits, while the latter amplifies the problem of light scattering and the absorptivity of the solvent used. Unlike the UV or visible spectra, solvent choice is severely limited in the IR region due to the nature of the measurement involved. Unfortunately, these problems are inherent, although alleviated somewhat by the use of lower concentrations and greater path length. Carbon disulfide, the solvent employed, aside from its toxic nature and flammability, presents additional handling problems due to its high volatility and relatively large coefficient of expansion. These and other considerations prompted us to seek a method of equivalent or greater specificity and rapidity, with greater accuracy, precision, and sensitivity than was previously obtained.

GLC fulfills all of the parameters necessary for a preferred analytical technique: simplicity, rapidity, precision, selectivity, accuracy, and sensitivity, provided the samples are of sufficient volatility for the technique to be applicable. Initial investigations met with little success, namely, poor resolution, long retention times, and nongaussian peaks.

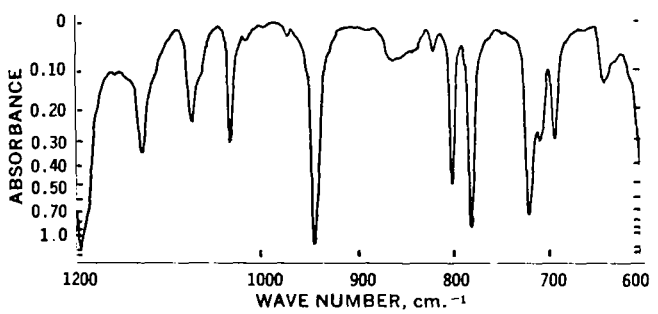

Figure 2—*IR spectrum of iodochlorhydroxyquin (6.04 mg./ml.) in carbon disulfide* versus *carbon disulfide in matched 3-mm. sodium chloride cells.*

Table II—Analysis of Synthetic Mixture of Quinolines by IR and GLC

Compound	Theoretical Percent	Percent Absolute Found—IR	Percent Absolute Found—GLC
5-Chloro-7-iodo-8-hydroxyquinoline	90.75	91.0	90.8
8-Hydroxyquinoline	0.92	Undetected	0.95
5-Chloro-8-hydroxyquinoline	2.35	2.0	2.2
5,7-Dichloro-8-hydroxyquinoline	5.99	12.1	6.1

The introduction of silylation as a useful chromatographic tool by Sweely *et al.* (7) in their investigations of sugars and related substances led us to pursue this possibility further. The major drawback to this procedure appeared to be the decomposition of trimethylsilyl reagents and derivatives by moisture. Of the silylating reagents studied, only *N*-trimethylsilylimidazole was usable without the need for rigid precautions to exclude moderate amounts of moisture from the system. This property and the reported lack of anomerization, smoothness of silylation, and reaction specificity with hydroxyl groups (8) were factors which determined our choice.

This procedure meets all of the conditions already discussed and is, we believe, a significant improvement over the method currently official in the USP XVIII and adapted by the NF XIII (9) for iodochlorhydroxyquin–hydrocortisone cream.

EXPERIMENTAL

IR—All spectra were recorded on a grating spectrophotometer[1]. A 4× abscissa expansion with a 25-min. scan time was employed and covered the range of 1200–600 cm.$^{-1}$. Absorptions were found to be reproducible to ±0.005 at an absorbance of 0.400 over the scanning range, with a wavelength reproducibility of ±5 cm.$^{-1}$ between 1200 and 600 cm.$^{-1}$. Resolution was 4 cm.$^{-1}$ at 1000 cm.$^{-1}$. Three-millimeter sodium chloride cells were used, with carbon disulfide (analytical reagent) in a 3-mm. sodium chloride cell as reference for all measurements. Sample purity determinations and calibration curves were carried out according to the procedure of Urbanyi *et al.* (3), and the calibration curves were found to be linear over the predicted ranges. The procedure was modified to the degree that absorbances were used directly in place of a semilogarithmic presentation of transmittance. Difficulty was encountered at high concentrations of the halogenated 8-hydroxyquinolines, particularly with those containing iodine substitution, the diiodo-8-hydroxyquinoline not being soluble much in excess of 0.3%.

GLC—A dual-column chromatograph[2], equipped with dual flame-ionization detectors, was used for all GLC work. Injection port and detector temperatures were 295 and 300°, respectively. Flow rates of 40 ml. He/min., 30 ml. H_2/min., and 300 ml. filtered air/min. (supplied by two Oscar's vibrator air pumps) were maintained. The columns were matched 1.83 m. × 0.32 cm. (6 ft. × 0.125 in.) Pyrex containing 3% methylsilicone (OV-1), 80–100 mesh on Varaport 30[3]. The injection ports contained glass liners, and the column was connected directly to the detector, resulting in

[1] Beckman IR 33.
[2] Varian Aerograph model 204B.
[3] Varian Aerograph Corp., Walnut Creek, CA 94598

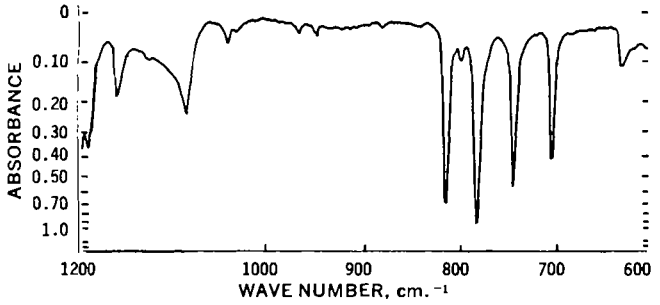

Figure 3— *IR spectrum of 8-hydroxyquinoline (1.51 mg./ml.) in carbon disulfide* versus *carbon disulfide in matched 3-mm. sodium chloride cells.*

an essentially all-glass system. Column temperatures under isothermal conditions were 230° where the determinations of diiodo-8-hydroxyquinoline, iodochlorhydroxyquin, or mixtures containing either of these were concerned or 192° where 5,7-dichloro-8-hydroxyquinoline, 5-chloro-8-hydroxyquinoline, or 8-hydroxyquinoline was of prime interest. Temperature programming at 6°/min. from 160 to 275° is useful for investigatory work, although isothermal operation was found to be more convenient for repetitive and/or routine analysis.

N-Trimethylsilylimidazole[4], I, was used as the silylating agent throughout. Samples were either 10 mg. of a solid mixture or 1 ml. of a 1% solution in pyridine analytical reagent (where synthetic mixtures were concerned). The silylation procedure was carried out in 6-ml. hypo-vials faced with Teflon disks, with no particular emphasis placed on avoiding moisture other than drying the vials prior to use. The sample (1.0 ml. in pyridine or 10 mg. solid) was transferred to the vial, 1.0 ml. of I was introduced, the vial was capped and crimped, the contents were shaken, and the resulting solution was allowed to stand at room temperature for 15 min. Silylation was found to be complete on solubilization (generally 5 min.), but 15 min. was allowed to ensure completion of the reaction and to allow for total elution of the previous sample from the column. A 0.8-μl. sample was injected using a 1-μl. syringe[5]. Calibration curves were determined by injecting 0.8 μl. of sample prepared by adding 1.0 ml. of I to 1.0 ml. of 0.2, 0.4, 0.6, 0.8, and 1.0% w/v solutions (of the halogenated 8-hydroxyquinoline) in pyridine, mixing, and allowing the resulting solution to stand at room temperature for 15 min. prior to injection. The response areas were found to be linear over the range noted. The addition of 1.0 ml. of 5-hydroxyquinoline (1.0% w/v in pyridine) as an internal standard to each of these solutions obviates the need for a constant injection volume and allows for direct comparison to a standard containing 5-hydroxyquinoline as an internal standard. For work where utmost accuracy is not necessary (*i.e.*, commercial samples where purity is in excess of 90%), it is sufficient to inject a sample after silylation, correct the area responses for individual molecular weights, and normalize the total corrected responses to 100%.

These techniques were compared and are reported under *Results and Discussion* (Table III).

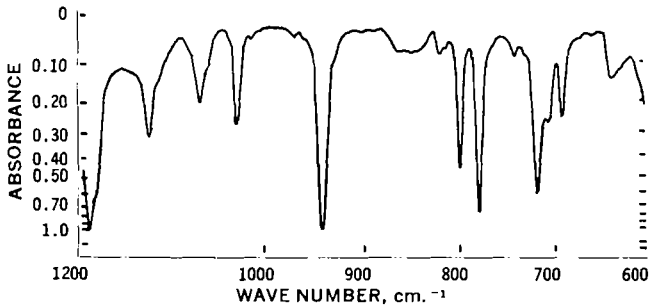

Figure 4—*Synthetic mixture of halogenated 8-hydroxyquinolines in carbon disulfide* versus *carbon disulfide in matched 3-mm. sodium chloride cells.*

[4] Pierce Chemical Co., Rockford, Ill.
[5] Hamilton No. 7107.

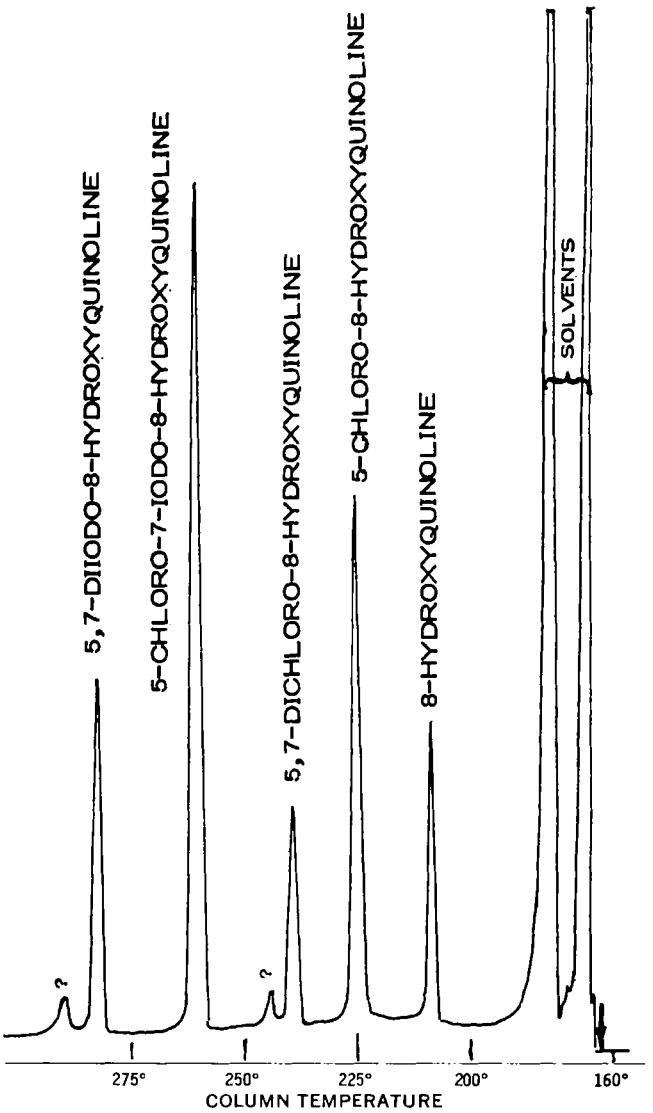

Figure 5—*Temperature-programmed (6°/min.) chromatogram of trimethylsilyl derivatives of synthetic mixture of 8-hydroxyquinoline and related halogenated 8-hydroxyquinolines.*

RESULTS AND DISCUSSION

The recorded IR spectrum of carbon disulfide in a 3-mm. sodium chloride cell is shown in Fig. 1 (a). Note that the background absorbances are significant, as evidenced when iodochlorhydroxyquin in carbon disulfide is superimposed (b). If the spectrum is recorded *versus* a matched 3-mm. cell containing carbon disulfide, the spectrum obtained is similar to that in Fig. 2. (The cells are essentially matched, giving resulting equivalent absorbance throughout the range.) The 40–60% transmittance range cited by Urbanyi *et al.* (3) as the area of greatest reproducibility corresponds to an absorbance range of approximately 0.220–0.400 and defines, based on laboratory determination of absorptivities, the minimum detectable quantities of impurities (assuming a 0.5% sample concentration as recommended by the authors) as listed in Table I.

It can be readily observed that significant quantities of impurities may be present, which may remain undetected if they fall below the levels of detection indicated.

The possibility that 8-hydroxyquinoline might be present in small concentrations in any halogenated 8-hydroxyquinoline prompted the determination of the effect, if any, of 8-hydroxyquinoline in the determination of the purity of iodochlorhydroxyquin. The spectrum (Fig. 3) indicates two absorption peaks at 813 and 741 cm.$^{-1}$ which might interfere with the determination of 5,7-dichloro-8-hydroxyquinoline (743 cm.$^{-1}$) and 5-chloro-8-hydroxyquinoline (823 cm.$^{-1}$). A sample was prepared containing 8-hydroxyquinoline, iodochlor-

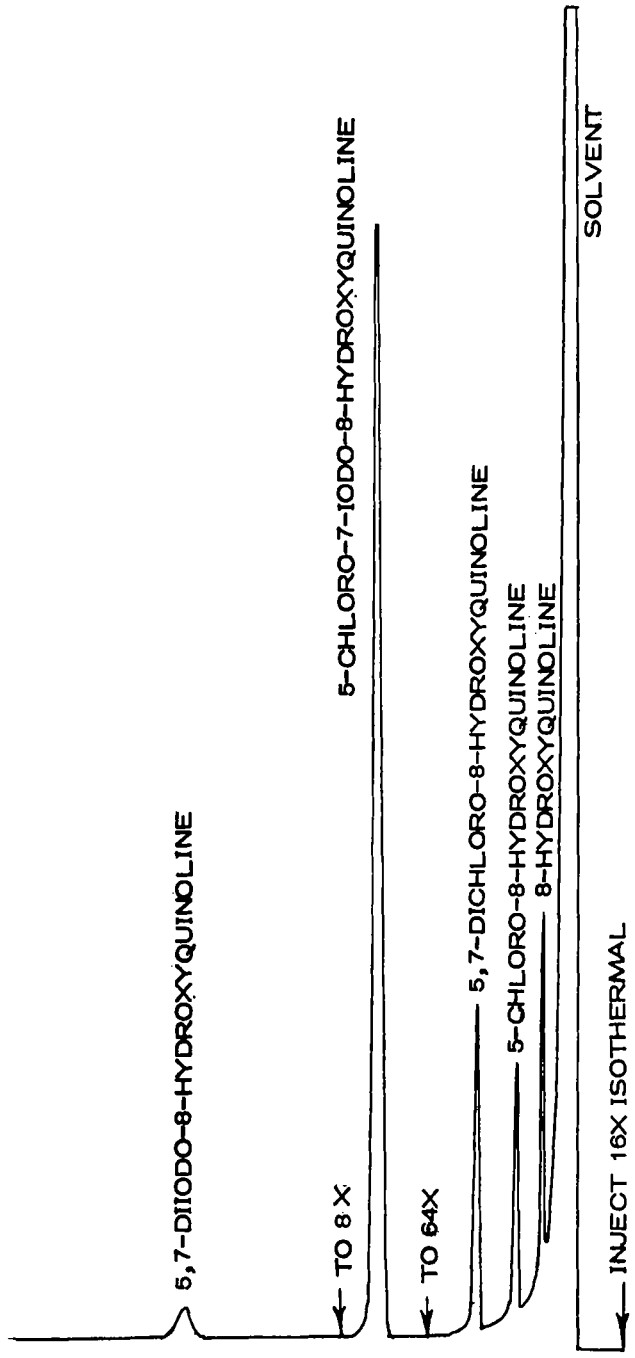

Figure 6—*Isothermal chromatogram of trimethylsilyl derivatives of synthetic mixture of 5-chloro-8-hydroxyquinoline and related 8-hydroxyquinolines* (T = *230°*).

hydroxyquin, 5,7-dichloro-8-hydroxyquinoline, and 5-chloro-8-hydroxyquinoline. Analyses were performed on these samples utilizing the IR and GLC procedures outlined. The results are tabulated in Table II and shown in Fig. 4.

It becomes obvious that a significant error in the determination of 5,7-dichloro-8-hydroxyquinoline is introduced as a direct result of the absorption at 741 $cm.^{-1}$ of the 8-hydroxyquinoline. The 5-chloro-8-hydroxyquinoline appears to be minimally affected.

The GLC procedure, on the other hand, provides greater selectivity, as evidenced in Figs. 5 and 6, the essential difference between the two chromatograms being temperature programming *versus* isothermal oven temperature. As a general procedure, isothermal operation was found to be simpler, more accurate, precise, and conducive to repetitive analysis. Sensitivities were checked with various mixtures, and detection limits of 0.1% and less were obtainable in all cases. As can be seen in Fig. 7, changes in column temperature allow for convenient analysis of other 8-hydroxyquinolines.

Response was found to be linear *versus* peak area to a maximum of 15 mg. of sample/ml. of reagent. This limit was fairly constant, regardless of the halogenated 8-hydroxyquinoline involved. The larger molecular weight introduced by substituting iodine for chlorine was not found to be significant, because this was accompanied by an overloading condition above the concentration limit. Responses were also found to be approximately equivalent with molar concentration and, in most cases, provided sufficient accuracy to obviate the need of standard response graphs.

It is significant that no problem was encountered with solubilities; whereas when the IR procedure is considered (particularly for diiodohydroxyquin), there is great difficulty in obtaining solution in carbon disulfide at the 0.3% level. Pyridine, on the other hand, is an excellent solvent and compatible with the silylating reagent employed in the GLC technique (although not usable in the IR as it is essentially opaque in the IR region of interest).

The addition of an internal standard was found to be unnecessary and sample size became inconsequential, with results being normalized to 100%. A mixture was prepared containing 8-hydroxyquinoline, 5-chloro-8-hydroxyquinoline, 5,7-dichloro-8-hydroxyquinoline, iodochlorhydroxyquin, and diiodohydroxyquin. This

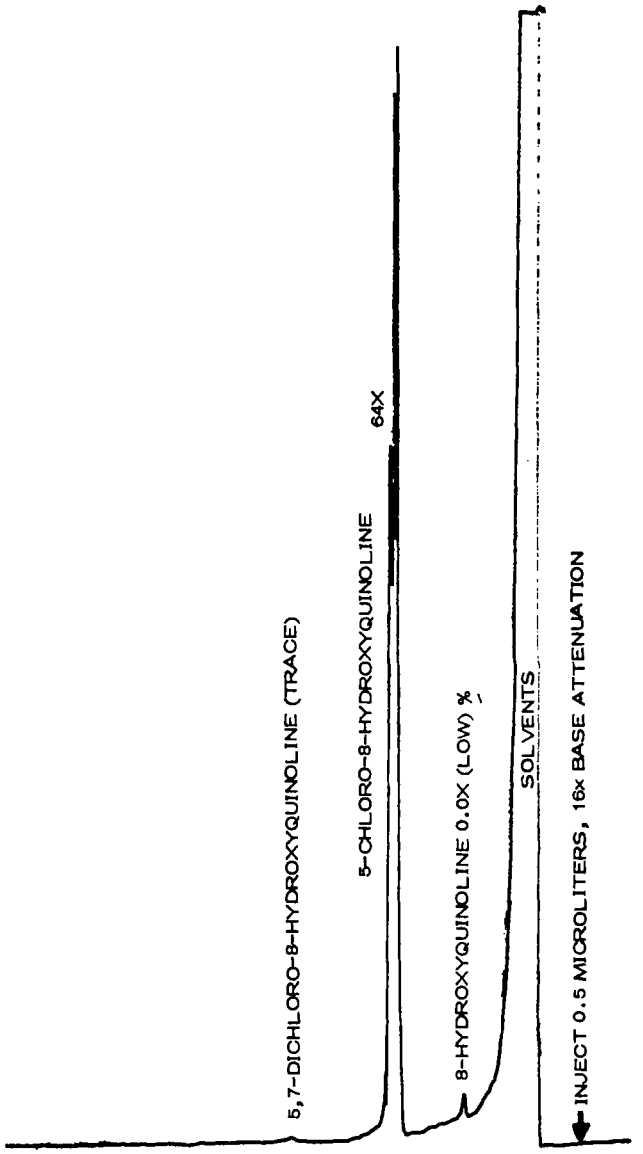

Figure 7—*Isothermal chromatogram of trimethylsilyl derivatives of 5-chloro-8-hydroxyquinoline* (T = *192°*).

Table III—Comparison of GLC Methods for Analysis of Trimethylsilyl Ethers of Halogenated 8-Hydroxyquinoline

Compound	Theoretical Percent	Percent Absolute Found (a)[a]	(b)[a]	(c)[a]
8-Hydroxyquinoline	8.46	8.5	8.8	8.3
5-Chloro-8-hydroxyquinoline	11.23	11.0	10.9	11.5
5,7-Dichloro-8-hydroxyquinoline	14.27	14.8	14.9	14.9
Iodochlorhydroxyquin	35.26	34.6	34.0	35.0
Diiodohydroxyquin	30.74	31.2	31.5	30.3

[a] Results obtained from: (*a*) standard graphs, (*b*) corrected areas, and (*c*) internal standardization and standard graphs (internal standard: 5-hydroxyquinoline).

sample was determined *via* GLC utilizing: (*a*) standard graphs, (*b*) area measurements (corrected for molecular weight), and (*c*) an internal standard (5-hydroxyquinoline). Results from (*a*) and (*b*) were normalized to 100%, while (*c*) was calculated on an absolute basis using standard graphs. Results are tabulated in Table III.

The sample used in Table II was run, after silylation, *via* GLC, using calculation (*b*) of Table III, with the results listed in Table II confirming the superior selectivity of the GLC procedure.

Previous investigations mentioned 5-iodo-8-hydroxyquinoline. We met with great difficulty in obtaining this material: upon receipt from the only source located, the sample was found to be mislabeled, being iodochlorhydroxyquin. Since, according to Urbanyi *et al.* (3), this constituent was not a major contaminant, no additional attempts were made to obtain it. However, it is probably present to a slight degree in certain diiodohydroxyquin samples (as noted by the unidentified peak in Fig. 8). The unidentified peak has a retention time similar to what one would expect from 5-iodo-8-hydroxyquinoline based upon all data recorded.

The silylation was found to be essentially complete within 5 min., although 15 min. was routinely used to ensure total reaction. Some decomposition became evident after 2 hr. of standing. Since the time between injections was approximately 15 min., samples were silylated between injections, if four or more were involved in the test series, to prevent erroneous results arising from possible degradation of silylated samples.

The singular problem involved with the GLC procedure is the necessity of detector cleanup because of a white coating which gradually deposits and is attributable to the silylated reaction products. Routine cleanup with solvents was performed every 2 weeks, without apparent loss of detector sensitivity noted between cleanings. This may be minimized by dilution of *N*-trimethylsilylimidazole to 1:5 or 1:10 with pyridine and subsequent use of 1.0 ml. of the resulting solution for silylation. However, as *N*-trimethylsilylimidazole is supplied in 1-ml. ampuls at a nominal cost and the cleanup was felt to be no more than a minute inconvenience, diluted reagents were not employed in this study. It is imperative, however, that a glass-lined injection port be used. Failure to do this will result in anomalous peaks being observed after a period of use which can be eliminated only by replacement of the injector port. This phenomenon was not apparent when stainless steel was used in place of glass for the column and appears to occur only during the transition from liquid to vapor phase in the injection port. Our experience is limited regarding the use of stainless steel columns with silylated materials; therefore, an all-glass system is recommended.

SUMMARY

The procedure presently employed by the USP XVIII for the identification and assay of iodochlorhydroxyquin is a significant improvement over that contained in earlier editions. However, it lacks the sensitivity to identify and quantitate impurities at relatively high levels and is subject to some interferences which can either invalidate or distort the results obtained. The rapid GLC procedure presented overcomes these difficulties as well as the solubility problems inherent in the IR procedure. Moreover, it provides sensitivities that are at least 5–20 times greater in the detection and identification of impurities, without loss of either accuracy or precision. Furthermore, the flexibility of the conditions allows the method to be extended to the USP monograph for diiodohydroxyquin, which still uses a procedure similar to that discarded for iodochlorhydroxyquin. It is conceivable that this technique can be readily adapted to the analysis of pharmaceuticals containing halogenated 8-hydroxyquinolines, and this investigative work is currently being carried out in our laboratory.

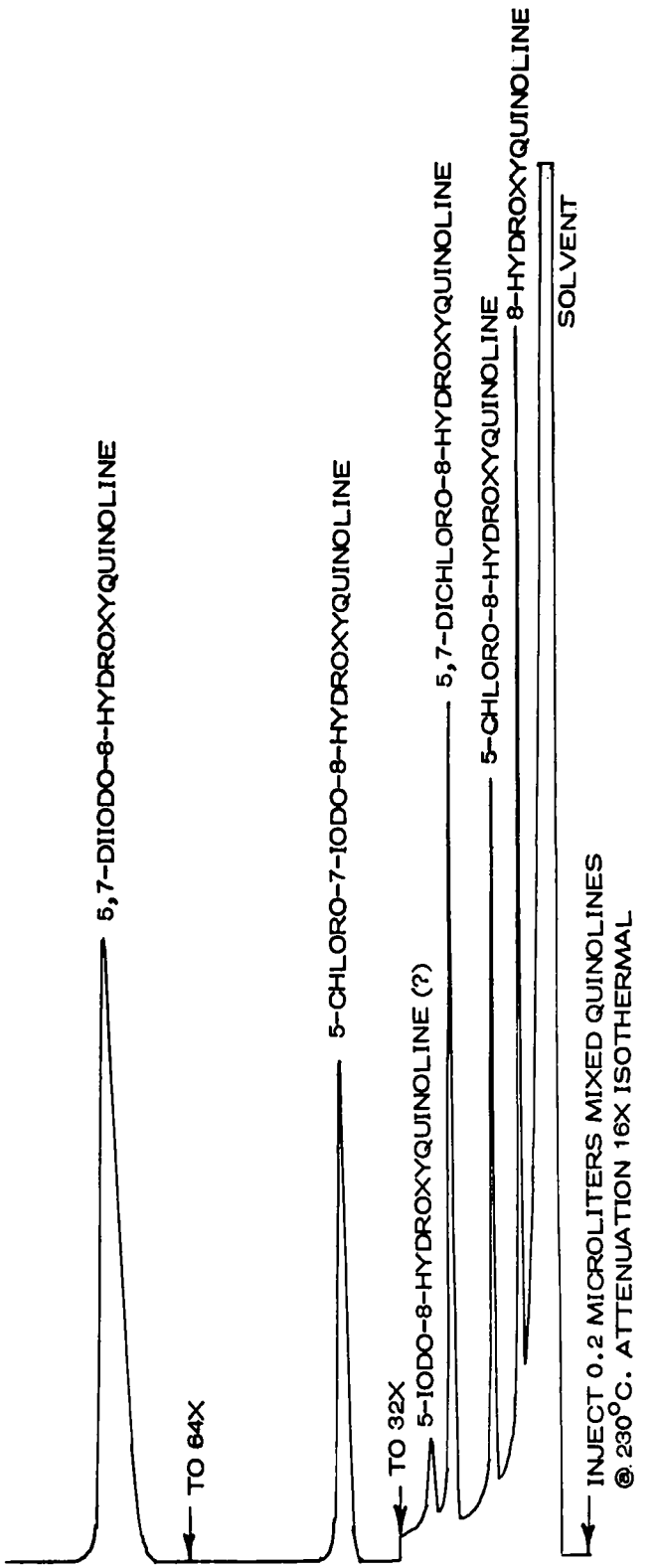

Figure 8—*Isothermal chromatogram of trimethylsilyl derivatives of a synthetic mixture of 8-hydroxyquinoline and related halogenated 8-hydroxyquinolines* (T = 230°).

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TECHNICAL ARTICLES

Dissolution Profiles for Capsules and Tablets Using a Magnetic Basket Dissolution Apparatus

R. E. SHEPHERD, J. C. PRICE▲, and L. A. LUZZI

Abstract □ Dissolution studies were carried out on commercially available dosage forms of lithium carbonate, 300 mg. A magnetic basket dissolution apparatus was developed by the authors because of the unavailability of a single system to evaluate both capsules and tablets. The magnetic basket allowed reproducible positioning of either a capsule or a tablet in a hydrodynamic system such that the dissolution of the two different dosage forms could be studied using the same parameters. Log-probability analyses of the data showed significant differences in the dissolution of the two dosage forms. The results were highly reproducible.

Keyphrases □ Dissolution profiles, capsules and tablets—magnetic basket dissolution apparatus and method □ Lithium carbonate tablets and capsules—comparison of *in vitro* dissolution rates, magnetic basket apparatus □ Magnetic basket dissolution apparatus—dissolution rates of both tablets and capsules □ Tablets and capsules—magnetic basket dissolution apparatus and method

During recent years it has become evident to pharmaceutical scientists and the Food and Drug Administration that dosage forms of the same active ingredients manufactured using different inert materials and different techniques may not bring about the same desired blood levels of active ingredient in the same time frame. Recently, for example, this was found to be the case for chloramphenicol capsules (1) when generic and trademark products were compared.

A number of variables affect the deaggregation of a tablet or capsule and the dissolution of a drug from these dosage forms (2–6). The rate of absorption of the drug is often directly proportional to the dissolution rate of the drug from the dosage form (2). Also, different dissolution rates from different dosage forms, *i.e.*, capsules and tablets, of the same strength are a probability even when emanating from the same manufacturer (7).

A method is needed for evaluating the dissolution rates for all drug products, whether in tablet or capsule form, using the same parameters. Literature dealing with the dissolution apparatus (6, 8, 9) shows that methods are not available which are applicable to both tablets and capsules and that particular methodologies are not capable of yielding reproducible dissolution profiles. For the USP XVIII the U. S. Pharmacopeial Committee adopted a dissolution procedure and apparatus for tablets and capsules in which a single-point determination is made for an active ingredient. Evaluation of the USP apparatus (USP XVIII, NF XIII, Method I) has shown that a "sieving" action by the screen takes place and that the screen may become clogged by granules or, in the case of capsules, by gelatinous particles (6, 9). An additional problem may be the inability to maintain homogeneity of the dissolution medium.

The NF XIII Dissolution Test Method II employs the USP–NF disintegration testing apparatus, except that 40-mesh screens are used. This device has been described as having a high agitation intensity and, therefore, has the disadvantage that small differences in formulation characteristics may not be revealed (9). In addition, the 40-mesh screen specified could lead to clogging, as in the USP–NF Method I.