TECHNICAL NOTE

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Identification of Dextropropoxyphene and Its Diastereoisomers

REFERENCE: Newby, N. R. and Hughes, R. B., **"Identification of Dextropropoxyphene and Its Diastereoisomers,"** *Journal of Forensic Sciences,* JFSCA, Vol. 25, No. 3, July 1980, pp. 646-654.

ABSTRACT: The specific diastereoisomer of a suspected propoxyphene sample can be identified by thin-layer chromatography, infrared spectroscopy, or nuclear magnetic resonance. If the sample is α-propoxyphene, the optical isomer must be identified by crystal tests, polarimetry, or melting point. This paper describes spectroscopic methods and physical properties that can be used to identify the four diastereoisomers and two racemates of propoxyphene. Of the four diastereoisomers, only the controlled α-*d*-propoxyphene and the noncontrolled α-*l*-propoxyphene forms are commercially available.

KEY WORDS: toxicology, propoxyphene, chemical analysis

It is essential for the forensic chemist to distinguish a compound from all other compounds regardless of physical or chemical similarities. Some compounds exhibit optical isomers as well as diastereoisomers. The propoxyphene molecule (Fig. 1) has two asymmetric centers, which give rise to four isomers arranged as two diastereoisomeric pairs, α- and β-propoxyphene. Since α-*d*-propoxyphene is the only form that became a controlled substance under the Controlled Substances Act of 14 March 1977 [*1*], it is necessary for the forensic chemist to identify this compound correctly.

It may take a combination of methods to distinguish one isomer from another. This paper discusses the adequacy of some of the techniques used in analytical chemistry to identify α-*d*-propoxyphene.

Experimental Procedures

An authentic sample of α-*d*-propoxyphene hydrochloride was supplied by Eli Lilly & Co., Indianapolis, Ind. The noncontrolled form, α-*l*-propoxyphene hydrochloride, was obtained by extracting an authentic sample of the napsylate salt, also supplied by Eli Lilly & Co., and converting it to the hydrochloride salt. The α-propoxyphene hydro-

Received for publication 20 March 1979; revised manuscript received 15 Nov. 1979; accepted for publication 17 Nov. 1979.

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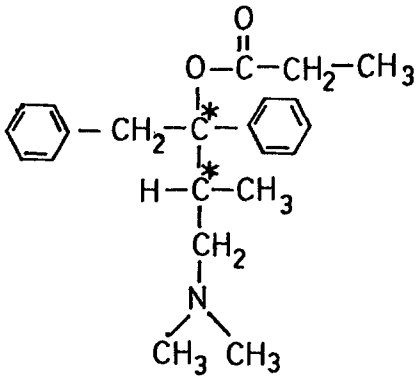

FIG. 1—*Propoxyphene molecule. The asterisks designate the asymmetric centers.*

chloride racemate was made from the authentic single optical isomer. Pure β diastereoisomers of propoxyphene were synthesized and purified by us as follows:

1. The procedure of Mannich and Heilner [*2*] in conjunction with that of Burckhalter and Fuson [*3*] was used to make a β-dimethylamino-α-methyl propiophenone hydrochloride.
2. The base formed by Procedure 1 was used to react with benzyl magnesium chloride to produce a mixture of the racemates of the α and β diastereoisomers of dimethylamino-1,2-diphenyl-3-methyl-2-butanol. The desired β racemate of dimethylamino-1,2-diphenyl-3-methyl-2-butanol was isolated by fractional crystallization. An alternative method has been developed by Allen and Cottrel,[2] who used high-pressure liquid chromatography with two micro-Porasil columns to separate the α and β forms of dimethylamino-1,2-diphenyl-3-methyl-2-butanol.
3. Another batch of the β racemates of this compound was prepared but it was further resolved by fractional crystallizations through the use of *d*-camphorsulfonic acid, similar to the method described by Pohland and Sullivan [*4*], into the optical isomers. The optically active carbinol hydrochlorides were prepared from their *d*-camphorsulfonic acid salts. These were each converted to their respective forms of β propoxyphene by the method of Pohland and Sullivan [*5*] and precipitated as the hydrochloride salts and recrystallized from ethyl acetate and ether. The reactions are shown in Fig. 2.

Melting Points

The melting points were measured by a Thomas Hoover UniMelt® capillary melting point apparatus and are uncorrected. Table 1 lists our experimental results.

Microcrystalline Tests

The reagent for the microcrystalline test, prepared according to literature instructions [*6*], is gold chloride in glycerol and water (1:9). Crystals formed were observed with polarized light for speed of formation, shape, and size.

[2]A. Allen and R. Cottrel, Drug Enforcement Administration, Southeast Regional Laboratory, Miami, Florida; personal communication, 1977.

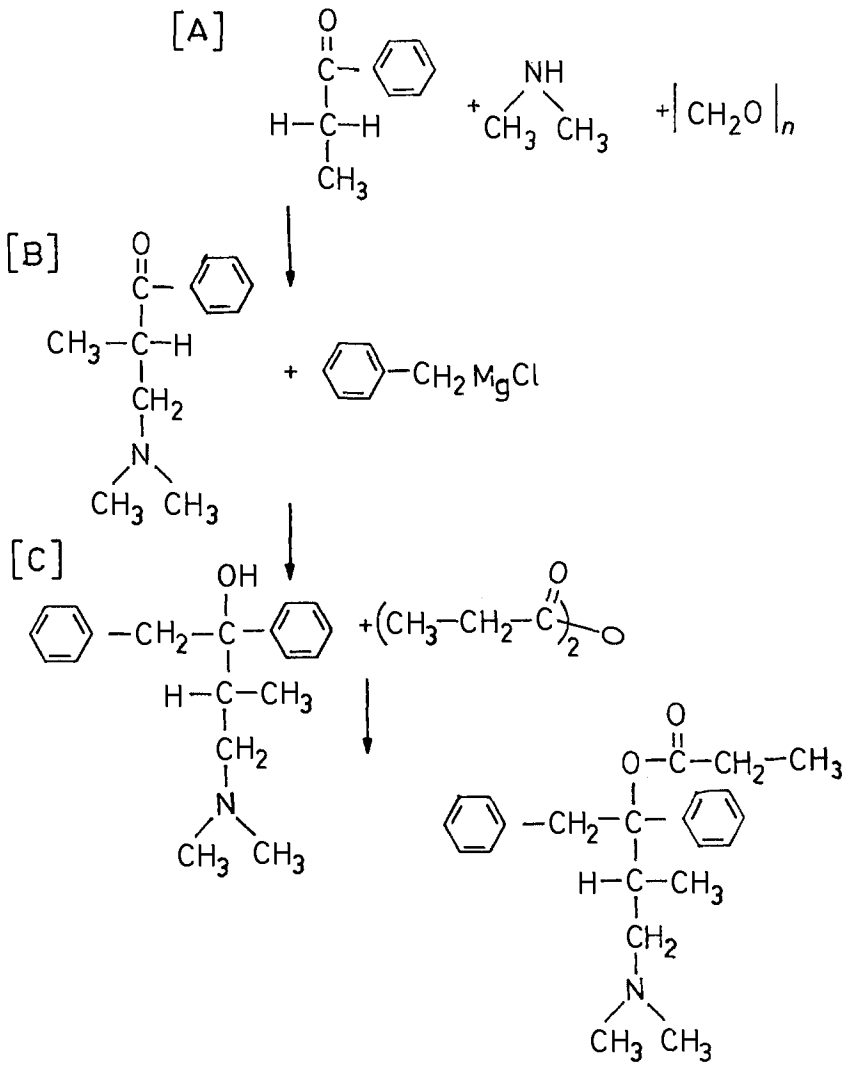

FIG. 2—*Synthesis of propoxyphene.*

TABLE 1—*Melting points of the diastereoisomers of propoxyphene hydrochloride.*

Compound	Melting Point, °C
α-*dl*	170-171
α-*d*	164-165
α-*l*	163-165
β-*dl*	196-197[a]
β-*d*	190[a]
β-*l*	189-190[a]

[a] The compound melted and then decomposed at this temperature.

Polarimetry

The direction and the amount of rotation are characteristic of each individual optically active compound. Literature values for the specific optical rotation of α-*d*-propoxyphene are shown in Table 2. The specific rotation for a 1% solution of α-*d*-propoxyphene should be between +52 and +57 [7].

Thin-Layer Chromatography

Precoated, silica gel GF, thin-layer chromatographic (TLC) plates were used in several developing solvents. The visualization agent was acidified iodoplatinate. Table 3 list the results of the TLC studies.

Infrared Spectroscopy

The infrared (IR) spectra were recorded on a Perkin-Elmer 457 Grating IR spectrophotometer. Figure 3 shows the spectrum of α-*d*-propoxyphene and Fig. 4, β-*d*-propoxyphene.

TABLE 2—*Specific optical rotation of α-propoxyphene hydrochloride (from Ref 8).*[a]

Optical Isomer	Rotation, $[\alpha]_D^{25}$
Dextro	+59.8[b]
Levo	−60.1[c]

[a]Where $[\alpha]_D^{25}$ is the specific optical rotation at 25°C for D (sodium) line.
[b]0.6 g of dextro form dissolved in 100 mL of water.
[c]0.7 g of the levo form dissolved in 100 mL of chloroform.

TABLE 3—*Thin-layer chromatography data.*

Compound	R_f Values				
	System 1[a]	System 2[b]	System 3[c]	System 4[d]	System 5[e]
α-*d*-Propoxyphene	0.41	0.66	0.61	0.73	0.42
α-*l*-Propoxyphene	0.41	0.66	0.61	0.73	0.42
α-*dl*-Propoxyphene	0.41	0.66	0.61	0.73	0.42
β-*d*-Propoxyphene	0.54	0.81	0.70	0.87	0.59
β-*dl*-Propoxyphene	0.54	0.81	0.70	0.87	0.59
β-*l*-Propoxyphene	0.54	0.81	0.70	0.87	0.59

[a]Acetone.
[b]Acetone/ether 30:70.
[c]Acetone/ether 50:50.
[d]Acetone/ether 70:30.
[e]Ether.

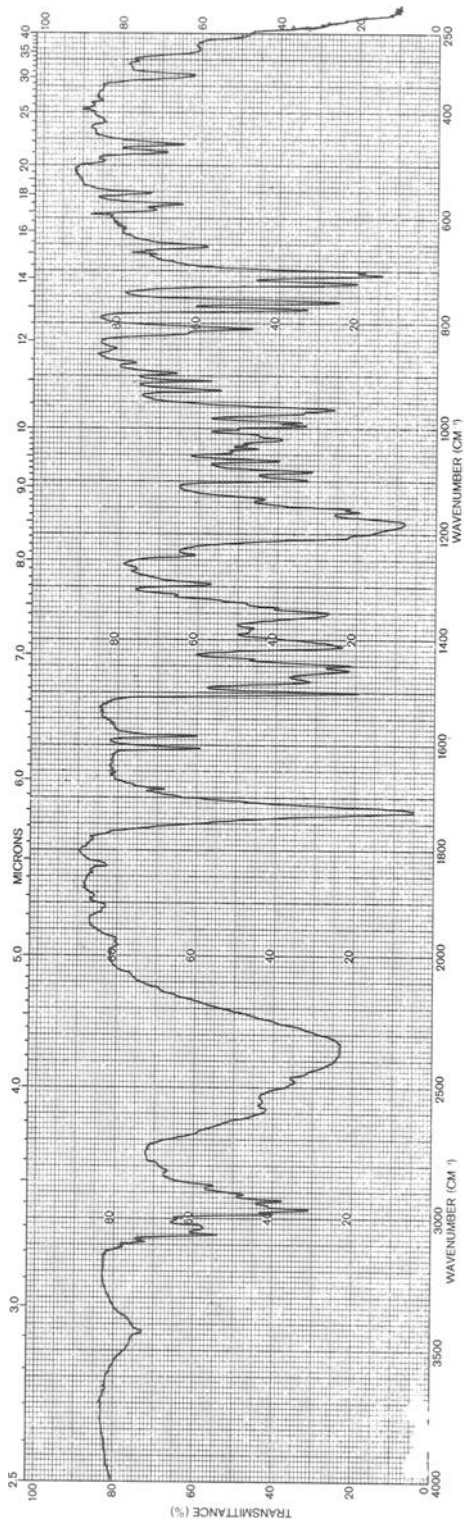

FIG. 3—*Infrared spectrum of α-d-propoxyphene hydrochloride.*

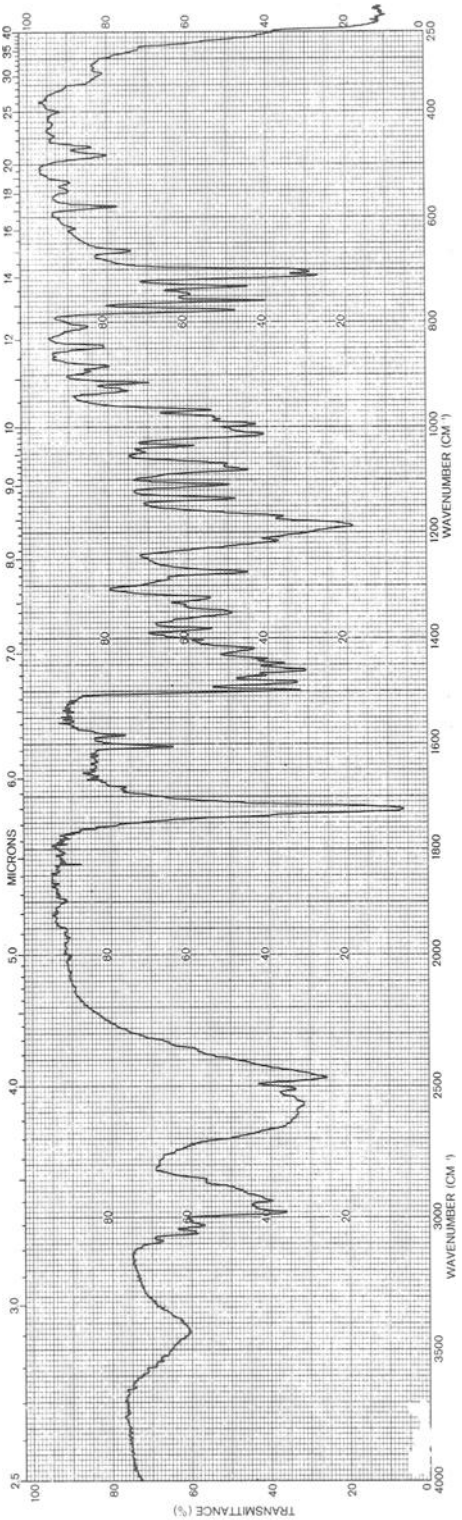

FIG. 4—*Infrared spectrum of β-d-propoxyphene hydrochloride.*

Nuclear Magnetic Resonance

The nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 390. Figure 5 shows the spectrum of α-*d*-propoxyphene and Fig. 6, β-*d*-propoxyphene.

Discussion

Nuclear magnetic resonance spectra were recorded on the EM 390 NMR spectrophotometer at 90 MHz. The spectra were examined as the hydrochlorides in deuterated chloroform. The spectra (Figs. 5 and 6) clearly show major differences between the α and β diastereoisomers of propoxyphene. The splitting patterns of the methyl protons (A and B in Fig. 7) can be used to differentiate between the diastereoisomers. In α-*d*-propoxyphene the methyl protons are clearly separated, giving rise to a triplet and doublet. The triplet and doublet in β-*d*-propoxyphene are barely separated. These two spectra graphically demonstrate the difference between the two diastereoisomers α-*d*- and β-*d*-propoxyphene hydrochloride. The spectra of β-*dl*- and β-*l*-propoxyphene hydrochloride were recorded but are not shown since they were identical with that of β-*d*-propoxyphene hydrochloride; also, the spectra of the α-*l* and α-*dl* forms were identical to that of α-*d*-propoxyphene hydrochloride.

The infrared spectra of the various diastereoisomers were recorded. When the α-*dl*, α-*d*, and α-*l* forms were compared, IR spectroscopy could not differentiate between a racemate and a single optical isomer, nor between optical isomers of α-propoxyphene hydrochloride. This finding was confirmed with β-propoxyphene hydrochloride when spectra of the β-*dl*, β-*d*, and β-*l* forms were compared. However, a comparison between α-*d*- and β-*d*-propoxyphene hydrochloride clearly demonstrated (Figs. 3 and 4) that it is possible to distinguish between α- and β-propoxyphene hydrochloride by the use of IR spectroscopy.

Examination of the TLC data presented in Table 3 shows that α- and β-propoxyphene

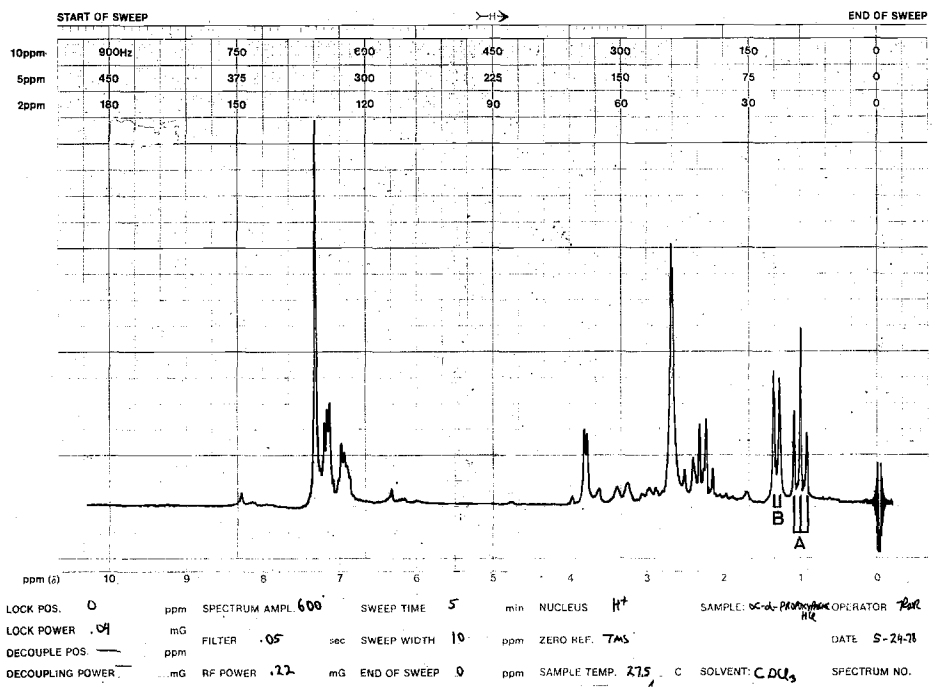

FIG. 5—*Nuclear magnetic resonance spectrum of* α-d-*propoxyphene hydrochloride.*

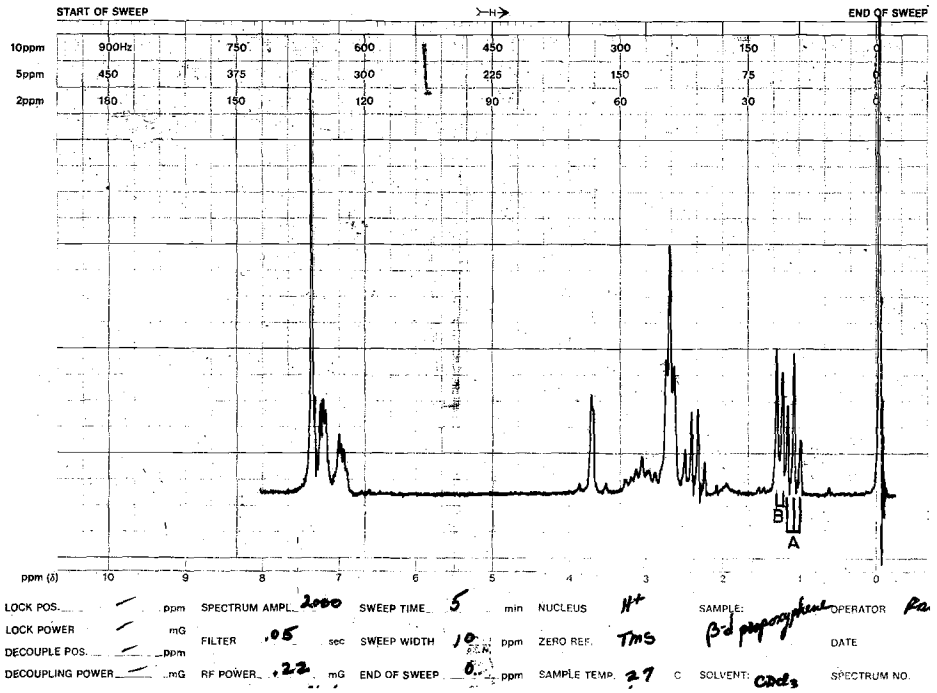

FIG. 6—*Nuclear magnetic resonance spectrum of β-d-propoxyphene hydrochloride.*

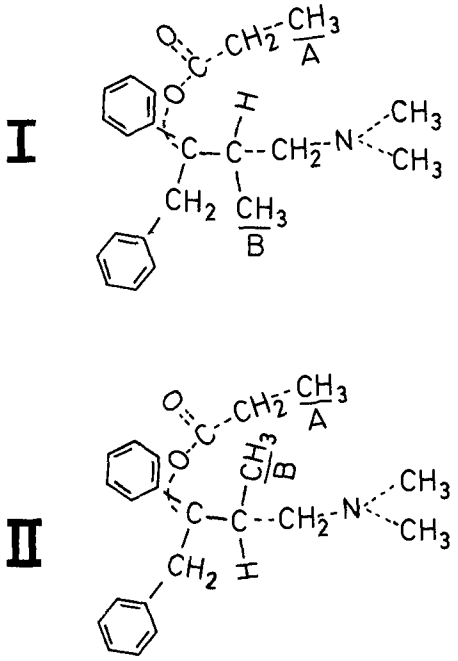

FIG. 7—*The splitting patterns of the methyl protons* (A *and* B) *differentiate β-propoxyphene* (I) *and α-propoxyphene* (II).

are clearly separated by using acetone, ethyl ether, or a combination of acetone and ethyl ether as the solvent system.

Based on our data (Table 1), determination of the melting point will distinguish between the α and β forms. Additionally, this test allows for differentiation between a single optical isomer and a racemate.

Once an exhibit is established as α-propoxyphene hydrochloride it must be shown that it is either the *d*- or *l*-isomer. This can be achieved by use of mixed melting points. After it has been determined that the substance is a single optical isomer of α-propoxyphene hydrochloride, an equal weight of α-*l*-propoxyphene hydrochloride is added. The sample is extracted and recrystallized and a new melting point determined. If the original optical isomer was α-*d*-propoxyphene hydrochloride, the *dl*-racemate will have been formed and the melting point will be elevated. If no change is observed in the melting point, then the sample was α-*l*-propoxyphene hydrochloride.

Since this method was time-consuming, two other methods were explored. With sufficient sample, optical rotation can be quickly measured with a polarimeter. Literature values are shown in Table 2. The specific rotation for a 1% solution of α-*d*-propoxyphene should be between +52 and +57 deg [*7*].

When small samples are encountered, a microcrystalline test may be more applicable; it requires minimal sample and is widely accepted.

The crystal test chosen was gold chloride in glycerol and water (1:9). The reagent was added to an aqueous drop of sample and evaporation allowed to occur. The single α optical isomer having straight needles considerably larger than those of the racemic form formed slowly (after 5 h), while the racemate having small, curved irregular needles, sometimes serrated, in bunches, or in branching chains, formed readily (in about 1 to 20 min). Clarke [*6*] essentially recommended this test for differentiation between a single isomer and the racemate. This test can be used to distinguish between the optical isomers by means of forming the racemate. A small drop of reagent containing the sample optical isomer is mixed with a drop containing an equal weight of known α-*l*-propoxyphene. If the racemate crystals form, then the sample contained α-*d*-propoxyphene. If the racemate crystals do not form, another drop of sample should be mixed with a drop containing an equal weight of known α-*d*-propoxyphene. The formation of the racemate crystals then establishes the sample as being α-*d*-propoxyphene. In the case of β-propoxyphene, crystals formed only with the *dl* racemate. The single optical isomers formed oil drops.

References

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[*5*] Pohland, A. and Sullivan, H. R., "Analgesics: Esters of 4-Dialkylamino-1,2-diphenyl-3-butanols," *Journal of the American Chemical Society,* Vol. 75, 1953, pp. 4458-4461.

[*6*] Clarke, E. G. C., "Note on the Differentiation Between Dextropropoxyphene and Laevopropoxyphene," *Journal of Pharmacy and Pharmacology,* Vol. 15, 1963, pp. 624-625.

[*7*] *The United States Pharmacopeia,* 18th revision, 4630 Montgomery Ave., Bethesda, Md., 1970, p. 556.

[*8*] *The Merck Index,* 9th ed., Merck & Co., Rahway, N.J., 1976, pp. 5315 and 7627.

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