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Liquid Chromatographic Determination of the Enantiomeric Composition of Methamphetamine Prepared from Ephedrine and Pseudoephedrine

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Determination of the stereochemical makeup of forensic samples can provide information about the source of the sample and a basis for intersample comparisons. The clandestine synthesis of methamphetamine and related amines continues to be a major source of these drugs of abuse. Most synthetic methods employ carbon–nitrogen bond formation and produce a racemic mixture; however, the individual enantiomers of ephedrine and pseudoephedrine contain the structural components of methamphetamine in chiral form. This paper will focus on the stereochemical course of the synthesis of methamphetamine via hydrogenolysis of the benzylic hydroxyl group in ephedrine and pseudoephedrine. The configurations of these amines were determined by liquid chromatography on an achiral C_{18} stationary phase following precolumn derivatization with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate.

The resolution of enantiomers by liquid chromatography is rapidly becoming a routine technique in many laboratories. Most of these methods involve interactions between a heterochiral sample and a homochiral ligand resulting in diastereoisomeric products. The various experimental forms of this process include the formation of either dissociable complexes or covalent diastereomers. The formation of dissociable diastereoisomeric complexes includes those chromatographic techniques that use chiral mobile-phase additives (*1*) and the techniques that utilize chiral stationary-phase materials (*2*, *3*). The chiral stationary-phase approach involves dissociable complexation between the individual sample enantiomers and the chiral ligand on the stationary phase. Pirkle and coworkers (*2*) have developed several chiral stationary phases that have been used for the separation of various drug enantiomers (*4*). Recently, Hermansson (*5*) has reported the direct resolution of racemic drugs using an α_1-acid glycoprotein chiral stationary phase. The formation of covalent diastereomers usually involves precolumn derivatization of the sample enantiomers with a homochiral derivatizing agent (*6*). Numerous reagents have been used for the diastereomeric derivatization of compounds that contain reactive functional groups such as primary and secondary amines. The resulting diastereomers can be separated by use of conventional achiral stationary phases in either normal or reversed-phase procedures (*6*). The chiral derivatizing agent 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) produces diastereomeric thiourea derivatives upon reaction with racemic amines (*7*). The commercially available GITC is chemically and stereochemically stable, and the thiourea derivatives have a strong absorption spectrum in the ultraviolet (UV) range. Thus, this reagent is a convenient means for diastereomeric derivatization of chiral primary and secondary amines.

The clandestine synthesis of methamphetamine and related amines continues to be a major source of these drugs of abuse. Most methods for the synthesis of methamphetamine employ carbon–nitrogen bond formation reactions, generally between a ketone such as phenyl-2-propanone and methylamine under reducing conditions (*8*). When such methods are employed, methamphetamine is produced as a racemic mixture—

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equimolar amounts of both the more potent *S* enantiomer and the *R* enantiomer.

Recently, we obtained forensic samples that consisted of mixtures of optically pure (*S*)-methamphetamine and significant quantities of (*R,S*)-ephedrine. (*R,S*)-Ephedrine possesses the same stereochemistry as (*S*)-methamphetamine at the carbon bearing the methylamino substituent and differs from methamphetamine only in the presence of a benzylic hydroxyl group. These structural similarities suggested that the methamphetamine present may have been synthesized from (*R,S*)-ephedrine. This article reports the results of an investigation of the stereochemistry of methamphetamine synthesized from (*R,S*)-ephedrine. Additionally, we investigated the stereochemistry of methamphetamine derived from (*S,R*)-ephedrine, the enantiomer of (*R,S*)-ephedrine, and the methamphetamines prepared from the ephedrine diastereomers, (*S,S*)- and (*R,R*)-pseudoephedrine. The stereochemical outcome of these syntheses was determined by converting the product methamphetamines to diastereomers using the chiral derivatizing agent GITC. The GITC–methamphetamine derivatives were identified by separation using high-performance liquid chromatography with an achiral C_{18} stationary phase.

EXPERIMENTAL SECTION

Reagents and Chemicals. Samples of (*S*)-methamphetamine hydrochloride, racemic methamphetamine hydrochloride, (*S,R*)- and (*R,S*)-ephedrine, and (*S,S*)- and (*R,R*)-pseudoephedrine were obtained from Sigma Chemical Co., St. Louis, MO. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate was purchased from Polysciences, Warrington, PA. HPLC grade chloroform and methanol were obtained from J. T. Baker Chemical Co., Phillipsburg, NJ. HPLC grade tetrahydrofuran (THF) was from Fisher Scientific Co., Fair Lawn, NJ. All other chemicals were reagent grade and were used without further purification.

The pH 3.0 phosphate buffer was prepared by mixing 9.2 g of monobasic sodium phosphate (NaH_2PO_4) in 1 L of double-distilled water and adjusting the pH to 3.0 with H_3PO_4.

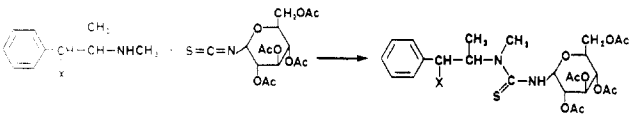
Instrumentation. The liquid chromatograph consisted of a Waters Associates (Milford, MA) Model 6000A pump, Model U6K injector, Model 440 UV detector with dual-wavelength accessory operated at 254 and 280 nm, and Houston Instrument (Austin, TX) OmniScribe recorder. Infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Model 1500 Fourier transform infrared spectrophotometer (FTIR). Nuclear magnetic resonance (NMR) spectra (^1H) were determined with a Varian T-60A spectrometer (Varian Instruments, Palo Alto, CA).

Chromatographic Procedures. Reversed-phase separations were carried out on a 30-cm × 3.9-mm-i.d. μBondapak C_{18} column (Waters Associates) at ambient temperature. The analytical column was preceded by a 7-cm × 2.1-mm-i.d. guard column dry packed with Co:Pell ODS (Whatman, Inc., Clifton, NJ). The mobile phases consisted of mixtures of THF, water, and acetic acid 35:70:1 (solvent system 1); methanol, water, and acetic acid 50:49:1 (solvent system 2); and pH 3.0 phosphate buffer and methanol 5:1 (solvent system 3). The mobile-phase flow rate was 1.5 mL/min, and the UV detector was operated at 0.2 AUFS.

Derivatization Procedure. To a separatory funnel was added 2 mg of each amine enantiomer to be studied. The amine was dissolved in 0.45 N NaOH and extracted as the base into chloroform. To the chloroform was added a 10% molar excess of GITC in chloroform. The reaction was allowed to proceed at room temperature for 10 min. The reaction mixture was then evaporated to dryness under a stream of air. The resulting residue was dissolved in 1 mL of THF or methanol, and 5 μL was injected into the liquid chromatograph.

General Method for the Preparation of the 1-Phenyl-1-chloro-2-(methylamino)propanes. A solution of the ephedrine hydrochloride or pseudoephedrine hydrochloride (1.65 g, 10 mol) and thionyl chloride (10 mL) in chloroform (200 mL) was stirred at reflux for 3 h. The reaction solution was then cooled to room temperature and the solvent volume reduced to approximately 50 mL. Addition of anhydrous ether (200 mL) followed by cooling (freezer) resulted in crystallization of the 1-phenyl-1-chloro-2-(methylamino)propane hydrochlorides.

Scheme I



General Method for Preparation of the Methamphetamines. A mixture of the 1-phenyl-1-chloro-2-(methylamino)-propane hydrochloride (500 mg, 2.3 mmol), sodium acetate trihydrate (1.22 g, 8.9 mmol), and 5% Pd–$BaSO_4$ (250 mg) in glacial acetic acid (95 mL) and water (5 mL) was shaken under a hydrogen atmosphere (initial psi of 40–45) on a Parr apparatus for 30–60 min. After the upake of hydrogen ceased, the catalyst was removed by filtration and washed with water (50 mL). The combined filtrate and water washings were evaporated to dryness under reduced pressure and the remaining oil dissolved in water (50 mL), and acidified with concentrated HCl (pH 1). The acidic aqueous solution was washed with chloroform (2 × 50 mL), then made basic (pH 12) with 10% NaOH. The basic aqueous solution was extracted with chloroform (3 × 75 mL), and the combined chloroform extracts were washed with water (100 mL) and dried over $MgSO_4$. Evaporation of the chloroform under reduced pressure yielded the product as the free base. The base was converted to the hydrochloride salt in ethereal HCl, and the salt was recrystallized from ethanol–ether to give a granular white solid.

RESULTS AND DISCUSSION

The identification of the individual enantiomers of pseudoephedrine, ephedrine, and methamphetamine can be accomplished by liquid chromatography following GITC derivatization. The isothiocyanate group in GITC is very reactive and undergoes nucleophilic attack by the amino group of primary and secondary amines to form thiourea products (see Scheme I). The derivatization reaction leads to products in high yield under mild reaction conditions. The free bases in chloroform solution are derivatized in about 10 min at room temperature. Figure 1 shows the separation of the GITC derivatives of these compounds and demonstrates the ease of identification of the individual enantiomers by this method. Maximum resolution and minimum analysis time were obtained by using a ternary solvent system of tetrahydrofuran, water, and acetic acid (solvent system 1).

The liquid chromatographic analysis of a recently obtained brown powder was accomplished by using reversed-phase techniques on a C_{18} stationary phase. The sample was found to contain ephedrine, methamphetamine, caffeine, and an unidentified component (Figure 2). Dosage forms containing this and similar mixtures of CNS stimulants are quite commonly received by forensic laboratories. Isolation of the basic fraction from this sample, derivatization with GITC, followed by HPLC analysis showed that the configurations of the amines were (*R,S*)-ephedrine and (*S*)-methamphetamine; the chromatogram also showed a third unidentified peak. Thus, the configuration is the same at the chiral carbon common to both the ephedrine and the methamphetamine in the sample (see Table I). These observations raised the possibility that the (*S*)-methamphetamine present in this sample was prepared from (*R,S*)-ephedrine.

Ephedrine and pseudoephedrine are readily available starting materials that contain the structural components of methamphetamine in chiral form. These compounds can be considered methamphetamines possessing a hydroxyl group at the benzylic position (carbon 1). Various synthetic methods have been described for the displacement of a benzylic hydroxyl group by hydrogen in compounds such as ephedrine (*10*). These reactions would result in the formation of methamphetamines from the ephedrines and pseudoephedrines. Theoretically, the methamphetamines produced would be expected to possess the same configuration at carbon 2 as

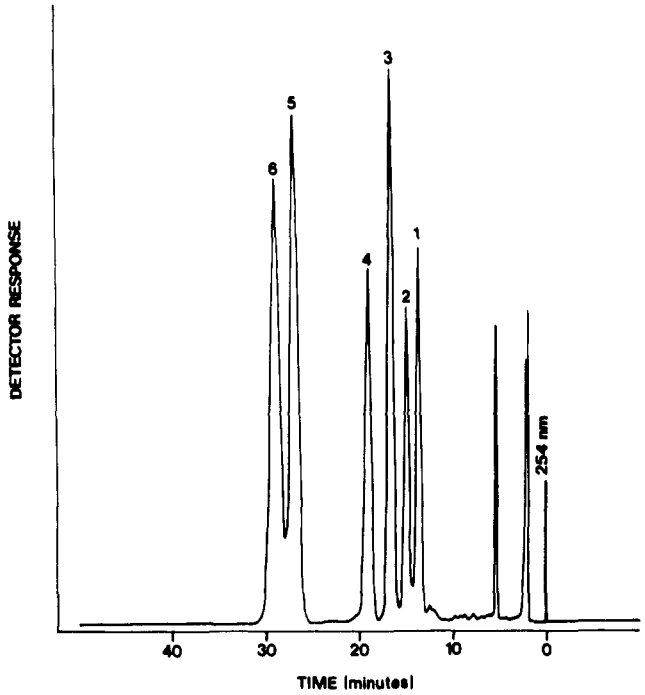
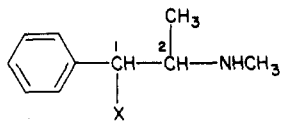


Figure 1. Liquid chromatographic separation of a mixture of GITC–amines containing (1) (*R*,*R*)-pseudoephedrine, (2) (*S*,*S*)-pseudoephedrine, (3) (*R*,*S*)-ephedrine, (4) (*S*,*R*)-ephedrine, (5) (*S*)-methamphetamine, (6) (*R*)-methamphetamine; solvent system 1.

Table I. Structures and Configurations of Amines in This Study



X	1	2	name
OH	*R*	*S*	(−)-ephedrine
OH	*S*	*R*	(+)-ephedrine
OH	*R*	*R*	(−)-pseudoephedrine
OH	*S*	*S*	(+)-pseudoephedrine
H		*S*	(+)-methamphetamine
H		*R*	(−)-methamphetamine

Table II. Melting Points and Yields of Intermediate 1-Chloro-1-phenyl-2-(methylamino)propanes and Product Methamphetamines

	intermediate 1-chloro-1-phenyl-2-(methylamino)-propanes[a]		product methamphetamine[a]	
substrate	mp, °C	yield, %	mp, °C[b]	yield, %
R,*S*-ephedrine	189–192	59	170–172	90
S,*R*-ephedrine	187–189	65	171–173	68
S,*S*-pseudoephedrine	185–190	64	166–167	80
R,*R*-pseudoephedrine	186–191	95	165–166	91

[a] NMR (^{1}H) and IR spectra were consistent with assigned structure. [b] Literature melting point is 170–175 °C (*9*).

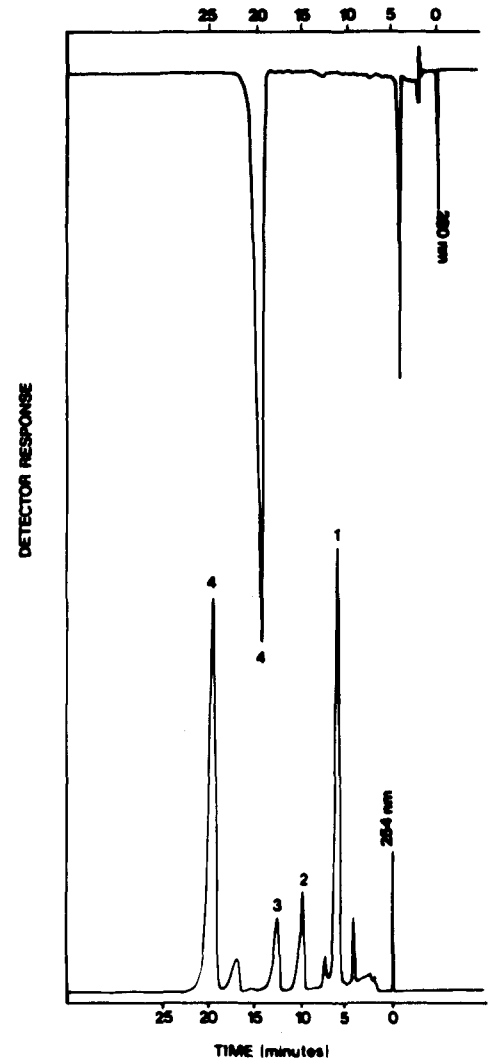
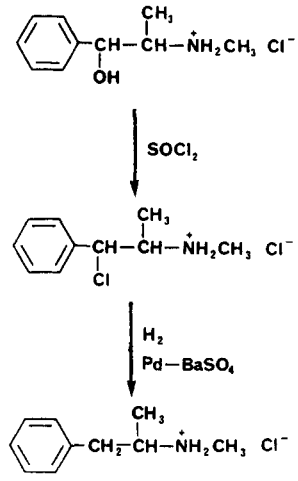


Figure 2. Liquid chromatographic analysis of a forensic sample containing (1) ephedrine, (2) methamphetamine, (3) unknown, and (4) caffeine; solvent system 3.

Scheme II



the starting ephedrine or pseudoephedrine. In this study, methamphetamines were prepared from each enantiomer of ephedrine and pseudoephedrine in order to establish the stereochemical course of such reactions.

Initial attempts to synthesize methamphetamines from ephedrine and pseudoephedrine by direct hydrogenolysis (50 psi) of the benzylic hydroxyl group resulted only in the recovery of the starting materials. One common method to further activate the benzylic position (carbon 2) is the formation of the corresponding benzyl chloride from the alcohols (*10*). This was accomplished by treating the ephedrines and pseudoephedrines with thionyl chloride in chloroform at reflux. The resultant benzyl chlorides readily underwent hydrogenolysis at medium pressure in the presence of palladium on barium sulfate to yield the methamphetamine hydrochlorides. The general reaction scheme used in these studies is outlined in Scheme II. Melting points and yields of the products from each reaction are given in Table II. The GITC

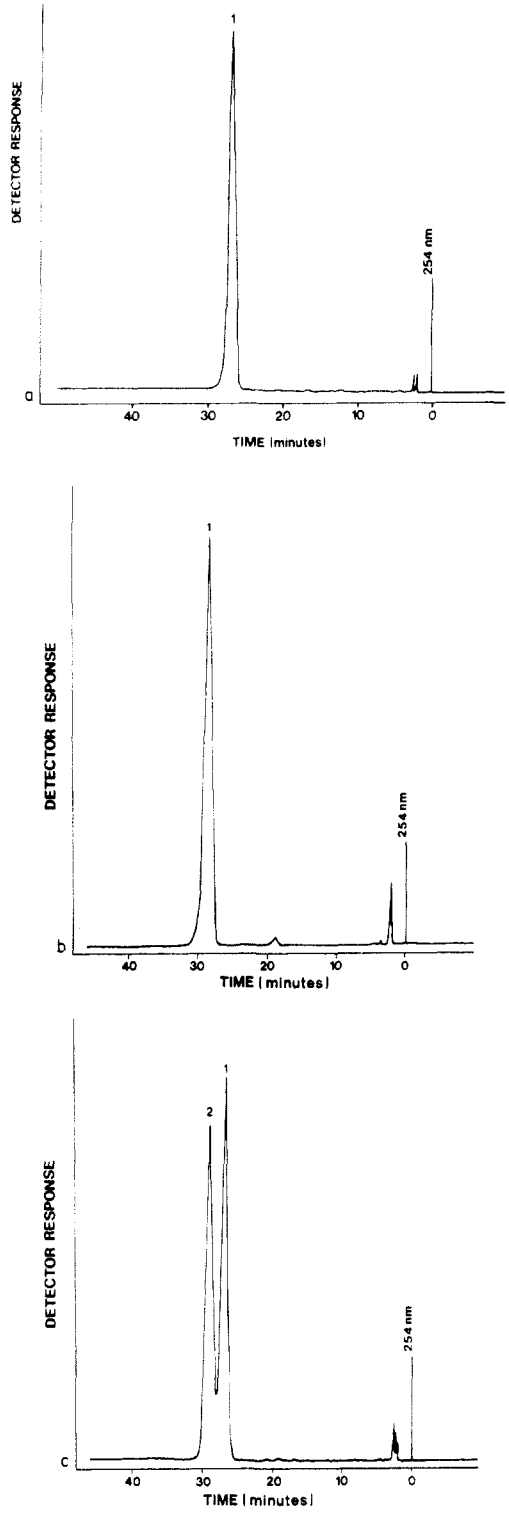


Figure 3. (a) Liquid chromatographic analysis of GITC-derivatized methamphetamine synthesized from (*R*,*S*)-ephedrine: (1) (*S*)-methamphetamine–GITC; solvent system 1. (b) Liquid chromatographic analysis of GITC-derivatized methamphetamine synthesized from (*S*,*R*)-ephedrine: (1) (*R*)-methamphetamine–GITC; solvent system 1. (c) Liquid chromatographic analysis of GITC-derivatized racemic methamphetamine: (1) (*S*)-methamphetamine–GITC, (2) (*R*)-methamphetamine–GITC; solvent system 1.

derivatization of the individual products produced the chromatograms in Figure 3. A single enantiomer of methamphetamine was obtained from each reaction, and confirmation of the structure of the final products was made by infrared and nuclear magnetic resonance (^{1}H) spectroscopy. The product methamphetamine in each case has the same absolute configuration at the 2-carbon as the substrate

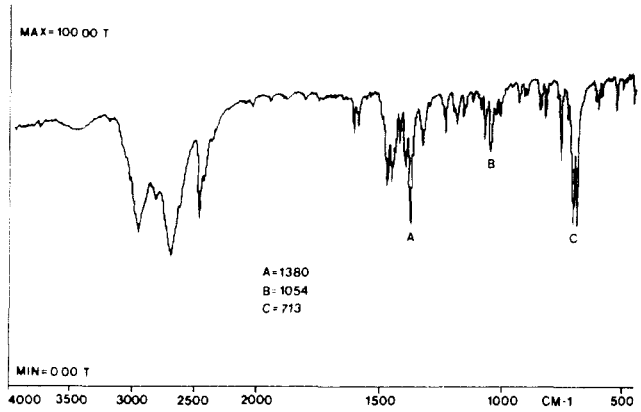
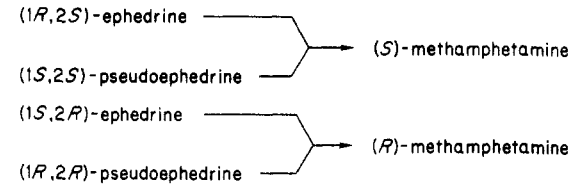


Figure 4. Infrared spectrum of the benzyl chloride product obtained from (*S*,*S*)-pseudoephedrine; KBr disk.

ephedrine or pseudoephedrine. Figure 3a shows that only (*S*)-methamphetamine is produced from (*R*,*S*)-ephedrine and an identical chromatogram was obtained from (*S*,*S*)-pseudoephedrine. Similarly, Figure 3b shows that only (*R*)-methamphetamine is produced from (*S*,*R*)-ephedrine and from (*R*,*R*)-pseudoephedrine. Thus, the reactions at the benzylic carbon do not appear to affect the configuration at the adjacent position. The stereochemical results of these studies are summarized as follows:



The chromatogram in Figure 3c is the result of GITC derivatization of a sample of racemic methamphetamine. This chromatogram illustrates the ease of chromatographic differentiation of the individual methamphetamine enantiomers by this procedure. All chromatograms in Figure 3 were obtained by using a mobile phase of tetrahydrofuran–water–acetic acid (solvent system 1).

In addition to the product methamphetamines, the stereochemical analysis of the intermediate benzyl chlorides was also undertaken. The infrared spectra of the benzyl chloride product from each enantiomer of ephedrine and pseudoephedrine were identical. The infrared spectrum of the benzyl chloride product obtained from (*S*,*S*)-pseudoephedrine is shown in Figure 4. If the replacement of the hydroxyl group of each enantiomeric ephedrine and pseudoephedrine occurred without racemization or inversion of configuration there would exist a diastereomeric relationship among the benzyl chlorides, and as diastereomers they would be expected to have different infrared spectra. Thus, the infrared analyses did not show any distinguishable characteristic among the benzyl chlorides and suggested that the same diastereomer was produced as the major product for all the reactions.

The liquid chromatographic analysis of the underivatized benzyl chlorides produced the chromatograms in Figure 5. Figure 5a shows the product benzyl chlorides from ephedrine, and Figure 5b shows the products from pseudoephedrine. The major and minor products from each of the four reactions have the same retention characteristics in this chromatographic system. However, the product distribution varies between the ephedrines and pseudoephedrines. These chromatograms indicate that the major product in each reaction is the same diastereomer. Proton NMR studies have been used to differentiate the threo (*R*,*R* and *S*,*S*) and erythro (*S*,*R* and *R*,*S*) diastereomers of ephedrine derivatives. For these compounds, it has been observed that the methine proton at carbon 1 in

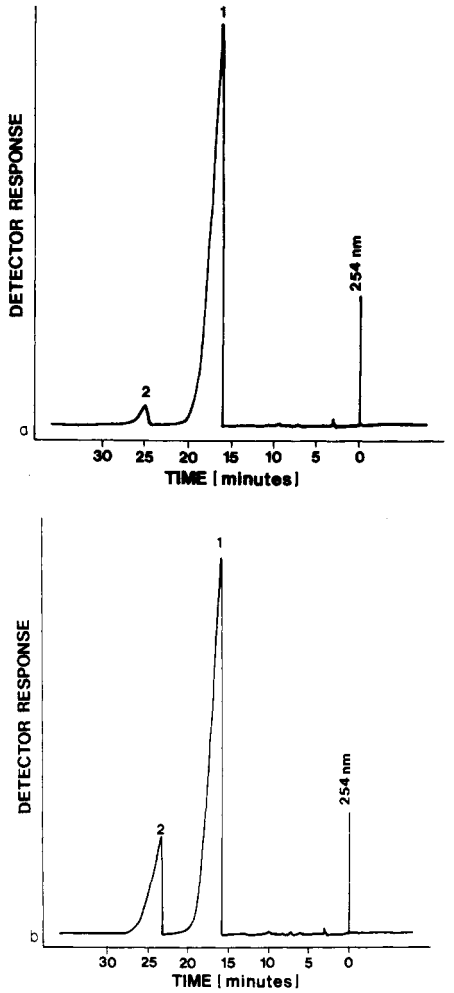


Figure 5. (a) Liquid chromatographic analysis of the diastereomeric benzyl chlorides obtained from (*R*,*S*)-ephedrine; solvent system 3. (b) Liquid chromatographic analysis of the diastereomeric benzyl chlorides obtained from (*S*,*S*)-pseudoephedrine; solvent system 3.

Table III. Stereochemical Relationships of Benzyl Chloride Intermediates to Ephedrine or Pseudoephedrine

substrate	benzyl chloride major (threo) + minor (erythro)	methamphetamine
R,*S*	*S*,*S* + *R*,*S*	*S*
S,*R*	*R*,*R* + *S*,*R*	*R*
S,*S*	*S*,*S* + *R*,*S*	*S*
R,*R*	*R*,*R* + *S*,*R*	*R*

the erythro isomers displays a higher chemical shift and smaller coupling constant than the corresponding proton in the threo isomer (*11*). Evaluation of the intermediate benzyl chlorides by proton NMR revealed that, in each case, the major product present is a threo isomer (δ = 5.5, J = 9.0 Hz). These studies also showed that more of the erythro isomers (δ = 6.0, J = 3.5 Hz) were formed from the pseudoephedrines than the ephedrines. From the studies on the configuration of the product methamphetamines, it has been established that the stereochemistry of the 2-carbon remains unaffected during the reaction sequence. Thus, the benzyl chloride intermediates have the stereochemical relationships to the substrate ephedrine or pseudoephedrine as shown in Table III.

The relationship between peaks 1 and 2 in each chromatogram (Figure 5) is diastereomeric; only the configuration at carbon 1 is affected by the reaction. For example, the chlorination of (1*R*,2*S*)-ephedrine can only produce the

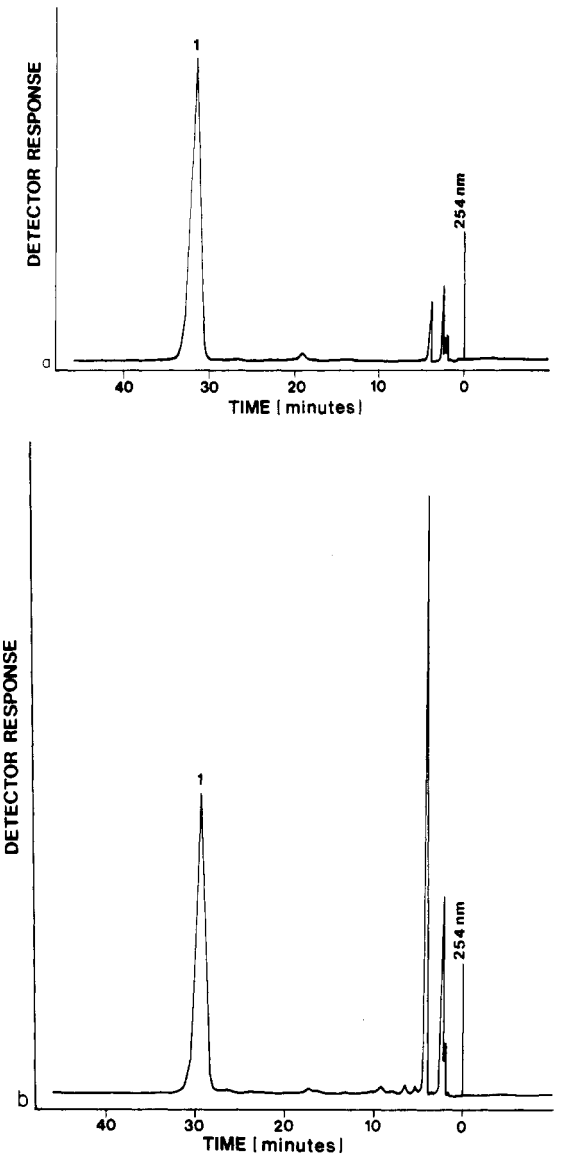


Figure 6. (a) Liquid chromatographic analysis of the GITC-derivatized benzyl chlorides obtained from (*S*,*R*)-ephedrine; solvent system 1. (b) Liquid chromatographic analysis of the GITC-derivatized benzyl chlorides obtained from (*S*,*S*)-pseudoephedrine; solvent system 1.

(1*S*,2*S*)-benzyl chloride or the (1*R*,2*S*)-benzyl chloride, and the relationship between these two compounds is diastereomeric, not enantiomeric. Furthermore, each of the two peaks in an individual chromatogram (Figure 5) can represent only a single enantiomer. Identical chromatograms are obtained from the chlorination of either (*R*,*S*)- or (*S*,*R*)-ephedrine (Figure 5a); however, peak 1 from (*R*,*S*)-ephedrine is enantiomeric with peak 1 from (*S*,*R*)-ephedrine since these intermediates produce methamphetamine of opposing configurations. The same is true for peak 2 in Figure 5a and analogously for the peaks in Figure 5b. Therefore, the major product of all four chlorination reactions is the enantiomeric pair of the threo diastereomer, and the minor product is the enantiomeric pair of the erythro diastereomer.

The stereochemical analysis of the intermediate benzyl chlorides was also undertaken by using the GITC derivatization procedure. HPLC analysis of the benzyl chloride–GITC derivatives from each enantiomer of ephedrine and pseudoephedrine produced the representative chromatograms in parts a and b of Figure 6. Figure 6a shows the chromatogram resulting from the GITC derivatization of the chlorination product from (*S*,*R*)-ephedrine; a chromatogram identical to Figure 6a was obtained from the product of (*R*,*R*)-pseudo-

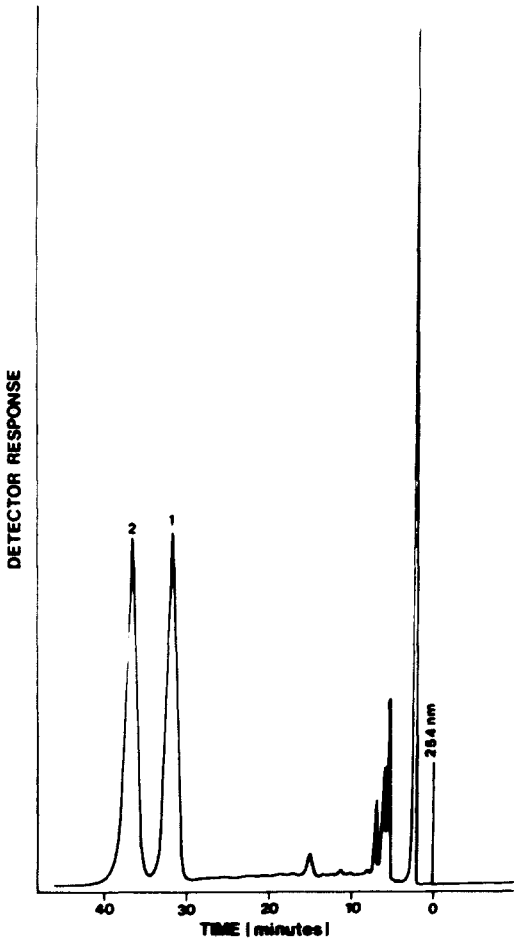


Figure 7. Liquid chromatographic analysis of the GITC-derivatized mixture of all benzyl chlorides: (1) benzyl chloride obtained from (*S*,*R*)-ephedrine and (*R*,*R*)-pseudoephedrine, (2) benzyl chloride obtained from (*R*,*S*)-ephedrine and (*S*,*S*)-pseudoephedrine; solvent system 2.

ephedrine. Figure 6b shows the chromatography of the GITC derivative of the benzyl chloride obtained from (*S*,*S*)-pseudoephedrine, and an identical chromatogram was obtained from the product of (*R*,*S*)-ephedrine. Derivatization with GITC should produce an individual peak for each enantiomer present in the reaction mixture. However, the minor erythro product (peak 2 in Figure 5) appears to decompose upon conversion to the free base and no GITC derivative was produced. These studies confirm that peak 1 in Figure 5 is present in both its enantiomeric forms. Figure 7 shows the GITC derivatization of a mixture of the benzyl chlorides obtained from all four reactions. Again, these chromatograms indicate the presence of only two major products: the two enantiomers of the threo diastereomer.

In conclusion, the unidentified peak in the original forensic sample (Figure 2) has now been identified as the intermediate benzyl chloride both by HPLC and IR. The GITC derivative of the benzyl chloride has retention characteristics identical to the major benzyl chloride product obtained from (*R*,*S*)-ephedrine. The presence of this compound shows that the clandestine manufacturing process involved chlorination of the (*R*,*S*)-ephedrine followed by displacement of the chlorine by hydrogen to yield (*S*)-methamphetamine. The stereochemical course of the conversion of an individual enantiomer of ephedrine or pseudoephedrine to methamphetamine occurs without affecting the chiral carbon common to both compounds. The threo diastereomer is the predominate form of the intermediate benzyl chloride regardless of the configuration of the starting material. A greater quantity of the minor erythro benzyl chloride is formed from the pseudoephedrines. Although the exact configuration of the benzyl chlorides was determined in this study, chirality at the benzylic position (carbon 1) is eliminated in the hydrogenolysis step. Thus, as long as the configuration at carbon 2 remains unaffected, both benzyl chloride diastereomers in a single reaction mixture produce the same enantiomer of methamphetamine.

Registry No. (1*R*,2*S*)-PhCH(OH)CH(CH_3)NHMe·HCl, 50-98-6; (1*S*,2*R*)-PhCH(OH)CH(CH_3)NHMe·HCl, 24221-86-1; (1*S*,2*S*)-PhCH(OH)CH(CH_3)NHMe·HCl, 345-78-8; (1*R*,2*R*)-PhCH(OH)CH(CH_3)NHMe·HCl, 670-40-6; (1*R*,2*S*)-PhCHClCH(CH_3)NHMe·HCl, 101859-98-7; (1*S*,2*R*)-PhCHClCH(CH_3)NHMe·HCl, 27270-80-0; (1*S*,2*S*)-PhCHClCH(CH_3)NHMe·HCl, 94133-42-3; (1*R*,2*R*)-PhCHClCH(CH_3)NHMe·HCl, 101859-99-8; (*R*)-$PhCH_2CH(CH_3)NHMe$·HCl, 826-10-8; (*S*)-$PhCH_2CH(CH_3)$NHMe·HCl, 51-57-0; (*R*)-$PhCH_2CH(CH_3)NHMe$, 33817-09-3; (*S*)-$PhCH_2CH(CH_3)NHMe$, 537-46-2.

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