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Chiral Analysis of Chloro Intermediates of Methylamphetamine by One-Dimensional and Multidimentional NMR and GC/MS

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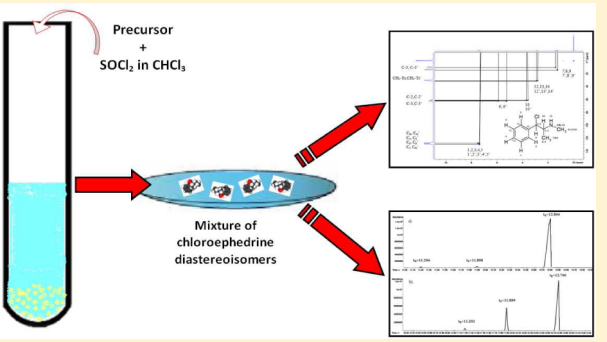
S *Supporting Information*

ABSTRACT: Impurity profiling and classification of abused drugs using chiral analytical techniques is of particular interest and importance because of the additional information obtained from this approach. When these methods are applied to the synthesis of illicitly used substances, they can supply valuable information about the conditions/chemicals used in the synthesis. We have applied GC and NMR methods to the study of intermediates found in methylamphetamine manufacture with the aim of linking the intermediates to the ephedrine/pseudoephedrine starting materials. Therefore, determination of the stereochemical makeup within samples of forensic interest is important giving further specific information to the analyst. This study investigates the stereochemical course of the Emde synthesis of methylamphetamine with particular focus on intermediate formation via the chlorination of ephedrine and pseudoephedrine enantiomers. The configurations of these chloro-phenethylamines were determined by 1D and 2D NMR analysis, and thereafter, the GC/MS analysis was carried out. We have shown here that chlorination of the ephedrine/pseudoephedrine compounds occurs via inversion (S_N2) and retention (S_Ni) of configuration around the α carbon and mixture of diastereoisomers (chloroephedrine and chloropseudoephedrine) were formed, with the ratio of the resulting compounds dependent on the precursors used. The preparation and analytical properties of these intermediate standards provide data for laboratories interested in the stereochemical analysis of methylamphetamine intermediates such as forensic/law enforcement, and illustrate the value of using a combination of analytical methodology.



A psychoactive drug is a loosely defined grouping of drugs that affect perception, mood, cognition, behavior, or consciousness. This is a result of changes in the functioning of the central nervous system.[1] The pharmacological classification and effects of psychoactive substances can be divided as follows:[2] neuroleptics, depressants, hallucinogens, and stimulants.

Stimulants are drugs that speed up the mind and body. Their effects resemble those of the body's natural hormones, adrenaline. But unlike natural hormones, stimulants can cause serious harm to the body.[3] Because stimulants bring about subjective changes in consciousness and mood that the user may find advantageous such as increased alertness or euphoria, many stimulants are abused and used excessively, despite the health risks or negative consequences. Recently, one of the most popular and widely abused within this class is methylamphetamine (MAM).

As is reported in the EMCDDA[4] (European Monitoring Centre for Drugs and Drug Addiction) and in the 2011 World Drug Report,[5] MAM is used to some extent in all European countries (notably the Czech Republic, the Republic of Moldova, and Slovakia), and is a huge problem worldwide particularly in the United States, southeast Asia, Australia, and New Zealand. Several countries report few but mostly industrial-sized operations, particularly in east Asia and parts of North America, existing for criminal profit.[4,5] This is because methylamphetamine has low production costs, easily obtained precursor chemicals, and a simple production process.[5]

The problems associated with MAM abuse are well reported not only in the media but also in the scientific literature.[6] Therefore, many national and international organizations such as the U.S. Drug Enforcement Agency[7] and The United Nations Office of Drugs[5] are concerned with these substances. Indeed, the stereochemical determination of MAM is a requirement in the U.S. since federal sentencing guidelines[8] carry a greater penalty for seizures containing >80% of the (+)-*S* enantiomer.

There are various routes to the synthesis of MAM, and they are illustrated in Figure 1. However, the most popular MAM

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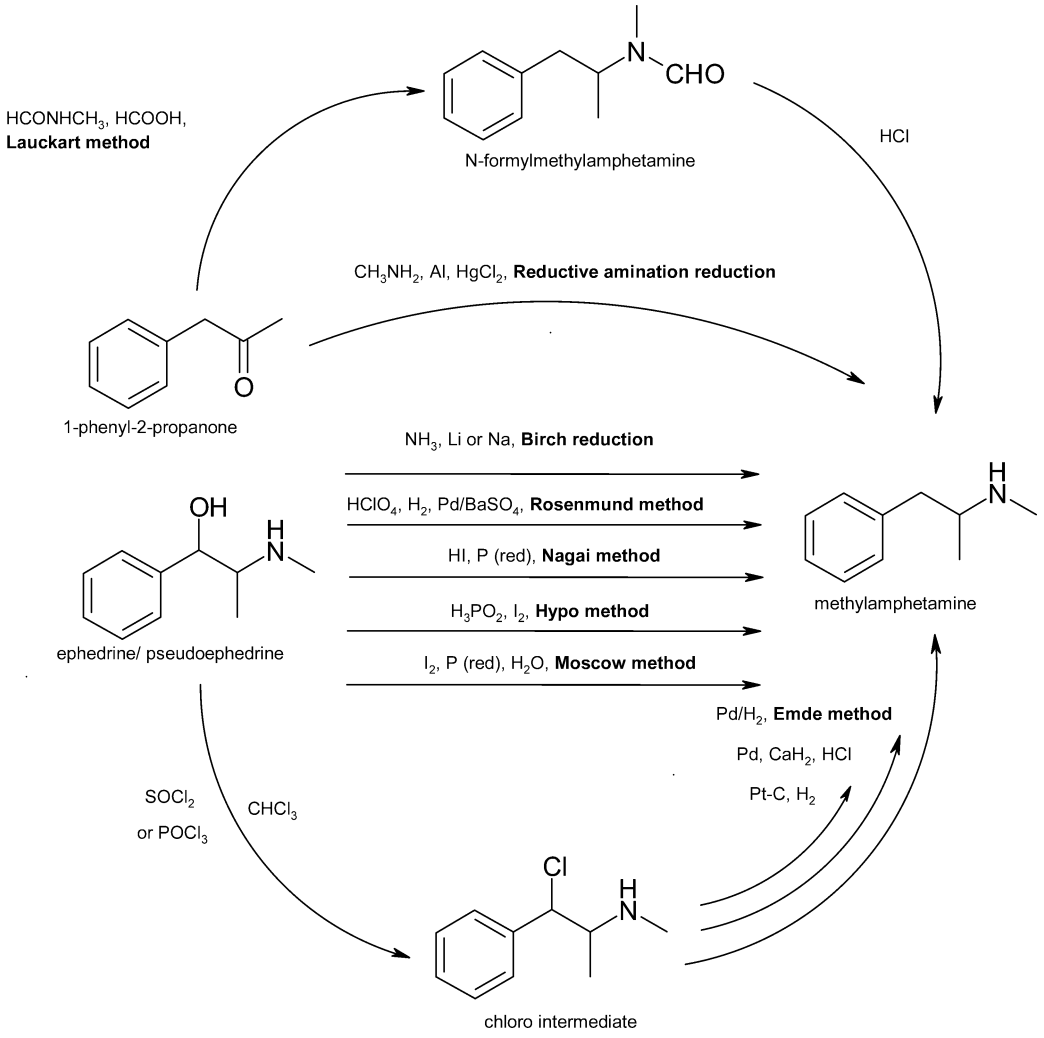

Figure 1. Common methods used to the manufacture of methylamphetamine.

synthetic routes (Birch, Nagai, and Emde method) employ ephedrine or pseudoephedrine as a precursor.[5,9]

Because the enantiomeric ratio of MAM is closely related with the optical activity of precursors and reagents used for the synthesis, this knowledge can provide useful information concerning the origins and synthetic methods used for illicit manufacture.[10] This information can be utilized for regulation of the precursors, investigation of the manufacturing sources, and resultant prevention of abuse. To obtain this information, analytical techniques which offer a high degree of enantioresolution are required.

It is reported that MAM synthesized by Emde contains the following byproduct: ephedrine, chloroephedrine, *cis*- and *trans*-1,2-dimethyl-3-phenylaziridine, and two unidentified impurities.[11,12] The stereochemical relationship of (*S*)-(+)-MAM to its initial precursor (1*R*,2*S*)-(−)-ephedrine or (1*S*,2*S*)-(+)-pseudoephedrine is achieved by detection of (1*S*,2*S*)-(+)-chloropseudoephedrine or *cis*-1,2-dimethyl-3-phenylaziridine, and (1*R*,2*S*)-(−)-chloroephedrine or *trans*-1,2-dimethyl-3-phenylaziridine, respectively (Figure S1).[11] Thus, knowledge about the chiral profile of MAM synthesized by Emde is important and may be a useful tool for both evidential and intelligence purposes.[13] Therefore, as previously described, to prevent the production of clandestine MAM, it is important to monitor, control, and evaluate the precursors of seized MAM.[14]

Impurity analysis for drug profiling has been used to enable the identification of the synthetic route for MAM manufacture from ephedrines. For example, route-specific impurities can be detected by HPLC and GC/MS.[15] Chiral analysis of seized MAM may also be useful, for example, whether the enantiomeric composition of intermediate suggests that the starting materials were extracted from pharmaceutical product (single enantiomers), the plant ephedra (mixture of enantiomers), or perhaps illicit ephedrine synthesized by fermentation processes.[15] The stereospecific separation of MAM can be approached using a variety of analytical techniques. The most commonly used are chromatography techniques: GC, LC, HPLC, and CE. There have been several reports that use of chiral stationary phases such as cyclodextrins and chiral derivatizating reagents greatly facilitates these methods.[16] For example, LeBelle et al.[17] investigated the chiral identyfication and determination of ephedrine, pseudoephedrine, methamphetamine, and metecatinone by both GC/MS after derivatization with (*R*)-(+)-methoxy-(α)-(trifluoromethyl)phenylacetic acid and nuclear magnetic resonance using a chiral solvating agent. GC/MS was shown to be capable of measuring the enantiomeric ratios of mixtures of these compounds. This study also shows that the analysis of compounds by NMR is also potentially useful for drug profiling. NMR spectroscopy has enormous potential for investigating conformations and configurations in organic

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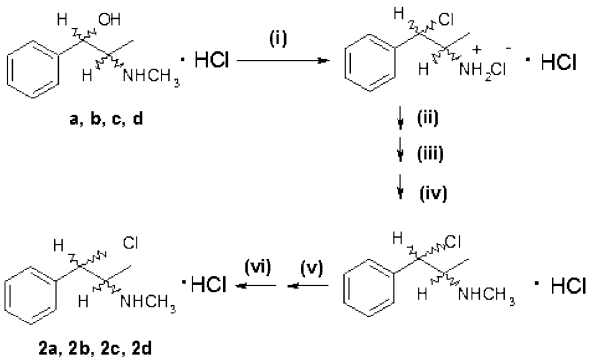
Scheme 1. Synthesis of the Chloro Intermediates of Methylamphetamine



a (-)-ephedrine, **b** (+)-ephedrine, **c** (+)-pseudoephedrine, **d** (-)-pseudoephedrine
2a, **2b**, **2c**, **2d** chloro intermediates of methamphetamine

Procedure[11]
(i) Step 1, $CHCl_3$, $SOCl_2$ (ii) Step 2, 70 °C, 5 h (magnetic stirring system) (iii) Step 3, 20 °C, evaporation to final volume of 50 ml (iv) Step 4, Et_2O, filtration (v) Step 5, MeOH, $(CH_3)_2CO$, 70 °C, recrystallisation (vi) Step 6, -5 °C, 24 h, recrystallisation

compounds as well as for quantitative analysis which has been shown by Matsumoto et al.[14] 1D and 2D hetero- and homonuclear NMR experiments enable complete assignment and structural information, and therefore can be useful when applied to chiral profiling of MAM and its derivatives.[15]

To create comprehensive characterization of MAM synthesized by the Emde in terms of impurity and chirality profile, which will provide a link between starting materials and the illicit MAM synthesized by the clandestine chemist, reference substances such as ephedrine derivatives and chloro-intermediates of MAM are required. Presently, pure enantiomers of ephedrine/pseudoephedrine are commercially available, but the four enantiomers of chloro intermediates are not available, meaning that the preparation of these compounds is required, and thereafter, separation into single enantiomers and purification is necessary.

Therefore, the purpose of this study was to investigate the stereochemical course of part I of the Emde method involving the synthesis chloroephedrine/chloropseudoephedrine via chlorination of ephedrine/pseudoephedrine. It is an extension of the work presented by Allen et al.[18] where products and intermediates of Emde synthesis for MAM were evaluated via ^{1}H NMR. In our research the configuration of the all of possible enantiomers of chloroephedrine and chloropseudoephedrine was determined by 1D and 2D NMR and thereafter by GC/MS.

This research was presented at the EUROanalysis 2011 (16th European Conference on Analytical Chemistry: Challenges in Modern Analytical Chemistry) in Belgrade.[19]

EXPERIMENTAL SECTION

Materials and Chemicals. (1*S*,2*R*)-(+)-Ephedrine HCl, (1*R*,2*S*)-(−)-ephedrine HCl, (1*S*,2*S*)-(+)-pseudoephedrine, (1*R*,2*R*)-(−)-pseudoephedrine, (*S*)-(+)-methylamphetamine HCl, (*R*)-(−)-deoxyephedrine, thionyl chloride, and trifluoroacetic anhydride were purchased from Sigma-Aldrich. Acetone, chloroform, diethyl ether anhydrous, methanol, and ethyl acetate were obtained from Fisher Scientific. Ethyl acetate was dried over type 5A molecular sieve from Sigma-Aldrich prior to use. Deuterated chloroform containing 1% (v/v) TMS for NMR analysis was obtained from Acros Organic. Helium and nitrogen (oxygen free) were supplied by BOC. Four chloroephedrine derivatives were synthesized by the first step of Emde with slightly modifications (outlined in Scheme 1).

Synthesis (Scheme 1). Chloro analogues of ephedrine were synthesized by the method of B. J. Ko et al.[11] Analysis was in agreement with published data for IR[20] and melting point.[21] The details are described in the Supporting Information (SI).

Recrystallization Procedure. Recrystallization procedure[22] is described in the SI.

IR Analysis. The IR spectra were obtained on a Perkin-Elmer FT IR spectrometer. Spectra of chloro analogues of ephedrine/pseudoephedrine have been recorded in the region 4000−400 cm^{-1}. The range (100−0% *T*) was correct.

Derivatization Procedure. Derivatization procedure was carried as described in the SI.

NMR Spectroscopy. Resonance spectra were recorded on a Bruker DPX 400 and Avance 400 NMR. Crystals of chloroephedrine in 1 mL of $CDCl_3$ containing 1% of TMS solution were dissolved. The solution was transferred to an NMR tube, and the spectra were recorded under conventional conditions.

Chromatography. Analysis was performed on a Hewlett-Packard 6890 GC and 5973 mass selective detector. Separation was achieved with a nonpolar capillary column (TR-5MS, 30 m × 0.25 mm i.d., 0.25 μm, Thermo Scientific, U.K.) with helium as the carrier gas at a constant flow rate of 1.8 mL/min. The oven temperature program started at 70 °C for 2 min, was increased to 250 °C at a rate of 10 °C/min, and then held at 300 °C for 2 min. A 1 μL aliquot of the derivatized sample was injected in the splitless mode with a purge time of 3 min. The injector and the GC interface temperatures were maintained at 200 and 250 °C, respectively. Mass spectra were obtained in the full scan mode over the range 40−500 *m*/*z*.

RESULTS AND DISCUSSION

For the experiment described here, four stereoisomers of ephedrine as starting materials were used to manufacture chloroephedrine derivatives by chlorination with thionyl

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chloride. The two chiral centers in these phenethylamines give rise to four stereoisomers. By convention the enantiomers with opposite stereochemistry around the chiral centers (1*R*,2*S* and 1*S*,2*R*) are designated chloroephedrine, while chloropseudoephedrine exhibits the same stereochemistry around the chiral carbons (1*R*,2*R* and 1*S*,2*S*).

Three mechanisms for the reaction of alcohols with thionyl chloride are proposed.[18] Typically, the reaction of alcohols with thionyl chloride proceeds via an internal nucleophilic substitution (S_Ni, Figure S-2a). The corresponding alkyl chlorides are produced. This method is known as Darzan's process and involves a two step reaction. First, thionyl chloride reacts with the alcohol to form an alkyl chloro sulfite, actually forming an intimate ion pair. Then, the concerted loss of a sulfur dioxide molecule has taken place, and thereafter, its replacement by the chlorides which was attached to the sulfite group. S_Ni results in final products which retain configuration of starting materials.[18]

A second possible mechanism is another two-step reaction. The first step is attack of the oxygen upon the sulfur of thionyl chloride, which results in displacement of chloride ion. Then, chloride ion attacks the carbon in bimolecular nucleophilic substitution (S_N2) fashion, resulting in cleavage of the C−O bond with inversion of configuration (Figure S-2b).[18]

Another possible route to the synthesis of chloroephedrine derivatives is a neighboring group mechanism, in which two successive S_N2 reactions (each with inversion of configuration) take place and the final stereochemistry is retained. First, inversion takes place when nitrogen attacks and forces out the leaving group, staying in its own position in molecule. The second inversion occurs after attacking of chloride.[18]

Therefore, four different stereoisomers could be expected during experiment. To differentiate the structure of chloro intermediates of MAM manufactured by first step of Emde, 1D and 2 D NMR have been used. To confirm these results, GC/MS was carried out.

Melting Point and IR Studies. After each synthesis the melting point was measured and compared favorably with literature values (Table S-1).[18] Completion of the reaction has been also followed by the IR spectroscopy. IR spectra confirm the conversion from ephedrine and pseudoephedrine enantiomers into chloride derivatives of these precursors. The resulting products do not contain hydroxyl groups but contain the characteristic peak originating from the chlorine which indicates that the reaction had occurred (Figure S-3).

^{1}H NMR Studies. NMR analysis was used to probe the conformations of the chloroephedrine derivatives (**2a**, **2b**, **2c**, **2d**) in solution. In spectra obtained for **2a** and **2b** there were six proton signals (described in SI). Considering these signals, the following structure (Figure 2) of sample analyzed can be deduced.

The spectra obtained for **2c** and **2d** show a different situation. Each proton signal is doubled which means that two stereoisomers are present in the sample. The signals of appropriate compounds are described in SI.

^{13}C NMR and DEPT Studies. For structure elucidation of the chloroephedrine derivatives, a series of NMR experiments including COSY, NOESY, DEPT were carried out. In the case of **2a**, **2b** compounds, there was the appearance of eight carbons in the ^{13}C NMR by DEPT experiments (Table 1). The spectra showed two methyl group proton signals, five methine signals, and additional one quaternary carbon signal coming from the aromatic ring. The ^{13}C DEPT NMR revealed two methyl, five methine, and one quaternary carbon signals for eight carbon atoms (Figure 3). The region from 127 to 137 ppm has been assigned to the carbon resonance of aromatic region, which is overlapped, with the carbon resonances (Cm, Cp, Co, Ci) of the aromatic region (C unit). The signals at 14 and 30.5 have been assigned to the methyl groups (C-3, CH_3-TS). The signals at 61 and 63 have been assigned to the methine carbon (C-2, C-1).

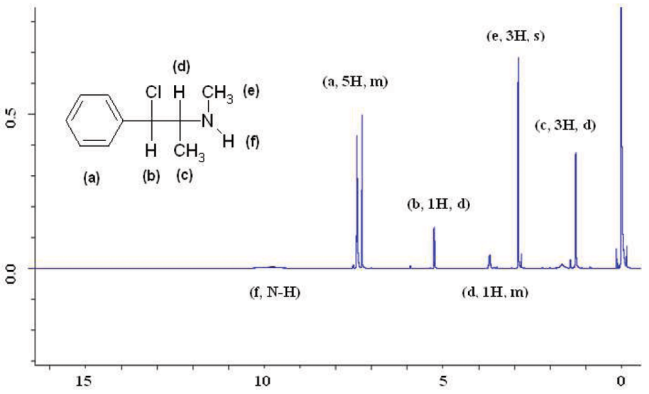

Figure 2. ^{1}H NMR spectra of chloro analogue synthesized from (1*R*,2*S*)-(−)-ephedrine.

The chloro analogues obtained from pseudoephedrine are not single enantiomers, and can be deduced from the more complicated ^{13}C NMR and ^{13}C NMR DEPT spectra. The ^{13}C DEPT NMR revealed 4 methyl, 10 methine, and 2 quaternary carbon signals for 16 carbon atoms. It can be concluded that two chloro analogues of ephedrine are present in the sample.

The results of the assignment of ^{13}C NMR and ^{13}C NMR DEPT spectra of **2a**, **2b**, **2c**, and **2d** at room temperature are summarized in Table 1.

COSY and HSQCED Studies. In Figures 4 and S-4, the COSY spectra for **2a**, **2b**, **2c**, and **2d** are given. The proton spectrum is plotted along each axis. The COSY spectrum shows a distinct set of spots on a diagonal, with each spot corresponding to the same peak on each coordinate axis. Lines have been drawn to identify the correlations. From the COSY spectrum of **2a** we can see that the protons of the methyl group (c) correlate with the methine proton (d). We can also see the correlation between methine proton (d) and another methine proton (b). The methyl group of the amine moiety (e) does not show off-diagonal peaks. COSY spectra for **2c** and **2d** are more complicated. Although the same correlation of corresponding protons can be seen, it also shows that each proton signal is doubled indicating the presence of two stereoisomers of chloroephedrine.

^{1}H−^{13}C HSQC NMR spectra were obtained to determine the direct carbon−proton bonds. The proton spectrum is plotted along the *x* axis, while the carbon spectrum is plotted on the *y* axis. Application of a ^{1}H−^{13}C HSQC pulse sequence allows the user to overcome the broad overlapping peaks in a one-dimensional proton spectra by dispersing the signals into the second ^{13}C dimension. ^{1}H−^{13}C HSQC NMR spectra are given in Figure 5. Lines have been drawn, and each hydrogen and carbon has been marked in order to facilitate the identification of correlations.

In the spectrum obtained for **2a** and **2b** the correlations between C1−H6, C2−H10, C3−H7,8,9, CH_3-Ts-H12,13,14, C_o,C_p,C_m-H1,2,3,4,5 are clearly observed. From the spectrum obtained for **2c** and **2d**, it can be seen that in the sample two stereoisomers of chloroephedrine are present. From a comparison of all the NMR data it can be concluded that samples **2a** and **2b** are single stereoisomers of chloroephedrine; product **2c**

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Table 1. ^{13}C NMR and DEPT NMR

	^{13}C NMR				DEPT			
	2a	2b	2c	2d	2a	2b	2c	2d
C-1	62.8742	62.8653	62.6623; 62.8305	62.6659; 62.8395	CH	CH	CH; CH	CH; CH
C-2	61.0642	61.0646	60.8687; 61.0269	60.8677; 61.0368	CH	CH	CH; CH	CH; CH
C-3	13.9854	13.9829	10.3556; 13.9821	10.3713; 13.9829	CH_3	CH_3	CH_3; CH_3	CH_3; CH_3
CH_3-Ts	30.4291	30.4186	30.4684; 31.0392	30.4583; 31.0481	CH_3	CH_3	CH_3; CH_3	CH_3; CH_3
Ci	136.9013	136.8974	136.3145; 136.9113	136.3163; 136.9189	CH	CH	CH; CH	CH; CH
Cp	129.2722	129.2734	128.8705; 129.2668	128.8715; 1292679	CH	CH	CH; CH	CH; CH
Co	129.6382	129.6422	128.9950; 129.6301	128.9975; 129.6313	CH	CH	CH; CH	CH; CH
Cm	127.7558	127.7554	127.4584; 127.7645	127.4585; 127.7643	C	C	C; C	C; C

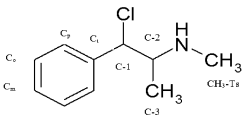

Figure 3. Structure of chloro intermediates of methylamphetamine with marked carbon atoms.

contains two stereoisomers of chloroephedrine, one of which is identical to sample **2a**; and product **2d** contains two stereoisomers of chloroephedrine, one of which is identical to sample **2b**.

SELNOESY Studies. To determine the mutual position/distance of protons in space, 1D SELNOESY NMR spectra were obtained by irradiating the anomeric proton signals H-e, H-c, H-b (more details in SI).

The NMR data from 1D SELNOESY showed that the compound synthesized from **1a** was (1*S*,2*S*)-(+)-chloropseudoephedrine, because we observed (1) large NOE correlation between H-e and H-c, large correlation between H-e and H-d, and weak correlation between H-e and H-b, H-e proton close to amine group; (2) strong NOE correlation between H-c and H-d, large correlation between H-c and H-e, and H-b, and weak correlation between H-c and H-a; (3) strong NOE correlation between H-b and H-a, large correlation between H-b and H-c, weak correlation between H-b and H-e, and any NOE correlation between H-b and H-d.

After analysis of 1D SELNOESY spectra obtained for **2a** and **2b**, it may be deduced that conversion of **1a**/**1b** to the chloro analogues occurred with inversion of configuration around the α atom to give one enantiomer, (1*S*,2*S*)-(+)-chloropseudoephedrine/(1*R*,2*R*)-(−)-chloropseudoephedrine, respectively, which is in accordance with an S_N2 mechanism. To confirm these results, GC/MS analysis was carried out.

All the NMR data showed that in the sample synthesized from **c** two stereoisomers are present. The first is the same as determined in the sample synthesized from **1a**, that is (1*S*,2*S*)-(+)-chloropseudoephedrine. The second diastereoisomer was determined as (1*R*,2*S*)-(−)-chloroephedrine, because we observed (1) large NOE correlation between H-e and H-c, large correlation between H-e and H-d, H-e proton close to amine group; (2) strong NOE correlation between H-c and H-d, large correlation between H-c and H-b, and large correlation between H-c and H-e; (3) strong NOE correlation between H-b and H-a, large correlation between H-b and H-d, and weak correlation between H-b and H-e.

Analysis of 1D SELNOESY spectra showed that conversion of **1c**/**1d** to the chloro analogues occurred with inversion and retention of configuration around the α atom to give two stereoisomers, (1*R*,2*S*)-(−)-chloroephedrine and (1*S*,2*S*)-(+)-chloropseudoephedrine/(1*S*,2*R*)-(+)-chloroephedrine and (1*R*,2*R*)-(−)-chloropseudoephedrine, respectively, in accordance with S_N2 and S_Ni mechanisms. To confirm these results, the GC/MS analysis was carried out.

GC-MS Analysis. GC/MS was carried out for qualitative analysis of synthesized analysis. Standards of the precursors,

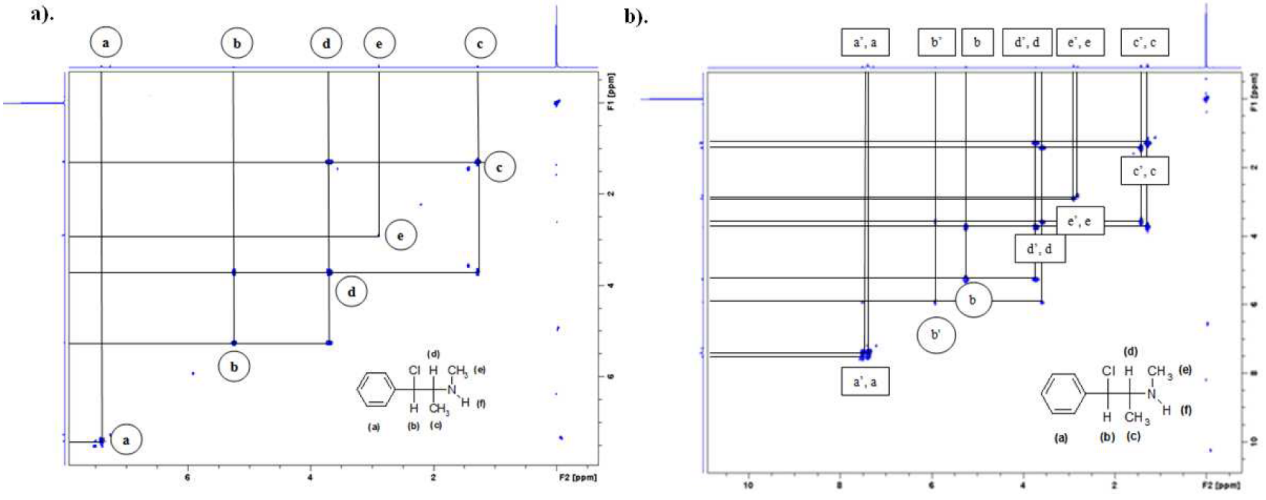

Figure 4. COSY NMR spectra obtained for (a) **2a** and (b) **2d**.

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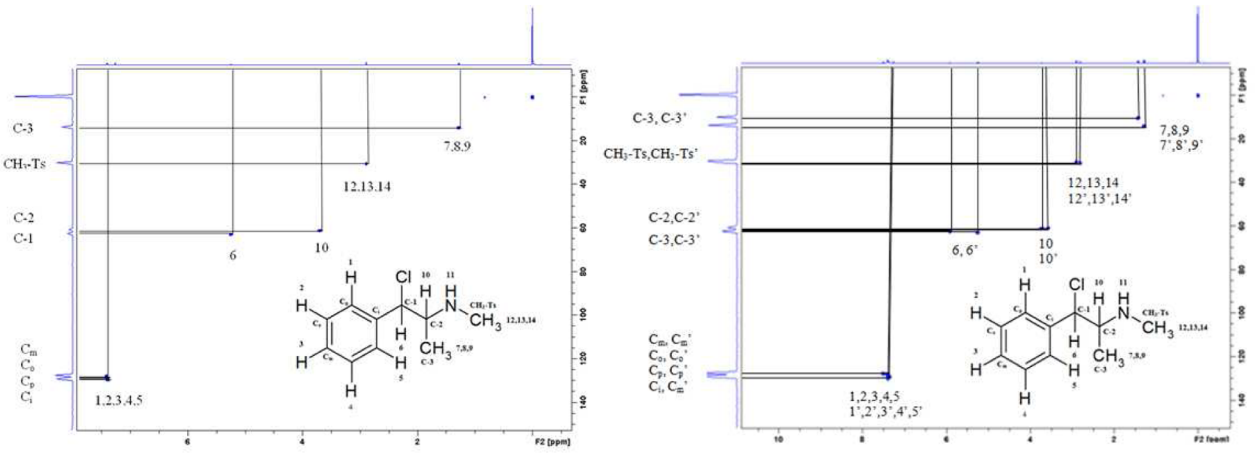

Figure 5. HSQC NMR spectra of chloro analogue obtained from (a) **1a** and (b) **1d**.

MAM, and samples **2a**, **2b**, **2c**, **2d** were trifluoroacetylated and analyzed individually. Retention times and mass-to-charge ratios are presented in Table S-2. Chromatograms and mass spectra obtained for **2a** and **2d** are shown in Figures 6 and 7.

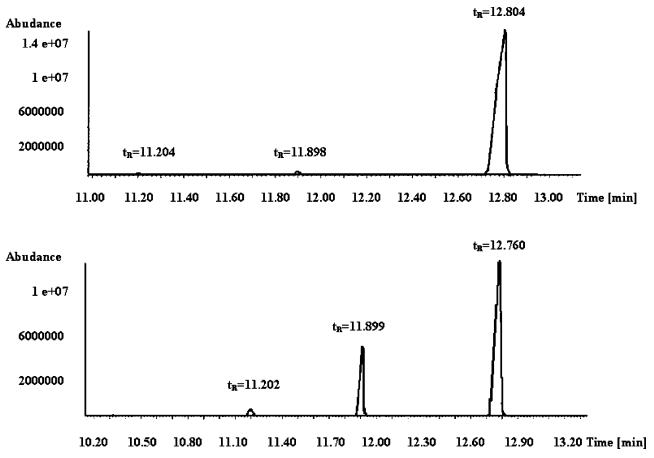

Figure 6. Chromatogram of analytes. Analytes are trifluoroacetylated derivatives of (a) (1*R*,2*S*)-(−)-ephedrine, (b) (1*R*,2*R*)-(−)-pseudoephedrine.

After analysis of GC/MS spectra, different conclusions than from NMR analysis may be deduced because, as is shown in Figure 6, all of the batches contained two diastereomers, while NMR only shows products obtained from pseudoephedrine enantiomers. Therefore, the chlorination of ephedrine enantiomers does not follow S_N2 completely as was shown in NMR, and in fact, a mixture of chloropseudoephedrine and chloroephedrine was determined, implying a mixture of S_N2 and S_Ni. Although the chlorination of pseudoephedrine enantiomers also occurred in accordance with S_N2 and S_Ni mechanisms to give a mixture of chloroephedrine and chloropseudoephedrine, the ratio of distereomers in **2a**, **2b**, **2c**, **2d** was dependent on precursors used for the synthesis. And so, the conversion of **1a**/**1b** to the chloro analogues occurred with inversion and retention of configuration around the α atom to give a mixture of 99% chloropseudoephedrine and 1% chloroephedrine (Figure 8). Conversion of **c**/**d** to the chloro analogues occurred also with inversion and retention of configuration around the α atom to give mixture of 20% chloroephedrine and 80% chloropseudoephedrine, in accordance with S_N2 and S_Ni mechanisms (Figure 9). The ratio of these diastereomers is different in comparison with literature values (Allen et al.[18]); however, the synthesis reaction in our work was carried out under different conditions (differences in the amount of reagents used, temperatures, time of synthesis, type of recrystallization) since a slight modification of synthesis in our work has been made. Moreover, the GC/MS data shows that one unidentified product was formed during synthesis (the mass spectral base peak of m/z 121).

CONCLUSION

Four stereoisomers of ephedrine as precursors were used to manufacture chloroephedrine derivatives by chlorination with thionyl chloride. After each synthesis, melting point, weight, and IR spectra were obtained. Melting point was compared with literature values, and in each case, values were consistent. IR spectra confirm the conversion from ephedrine into chloro-derivatives. The resulting products lack hydroxyl groups but contain the characteristic peak originating from the chlorine which indicates that the reaction had occurred.

1D NMR analysis was used to probe the conformations of the chloroephedrine derivatives in solution. The ^1H, ^{13}C, DEPT, COSY, and HSQC NMR spectra illustrate that depending on the precursor used it is possible to obtain a single enantiomer or a mixture of enantiomers. One-dimentional SELNOESY NMR data illustrate that conversion of ephedrine enantiomers to the chloro analogues occurred with inversion of configuration around the α atom to give one enantiomer, chloropseudoephedrine; however, the GC/MS result showed that mixture of diastereomers (1% chloroephedrine and 99% chloropseudoephedrine) is manufactured during this synthesis. Both NMR and GC/MS results obtained for samples manufactured from pseudoephedrines showed that conversion of pseudoephedrines to the chloro analogues occurred with inversion and retention of configuration around the α atom to give mixture of two: 20% chloroephedrine and 80% chloropseudoephedrine. Therefore, the ratio of the resulting compounds was depended on precursors used. Moreover, the GC/MS data demonstrate that one impurity was formed during synthesis.

The use of NMR and GC/MS analysis allowed the determination of conformations and configurations of manufactured chloroephedrine derivatives, and important and commercially unavailable chloro intermediates of methylamphetamine synthesized by the Emde method.

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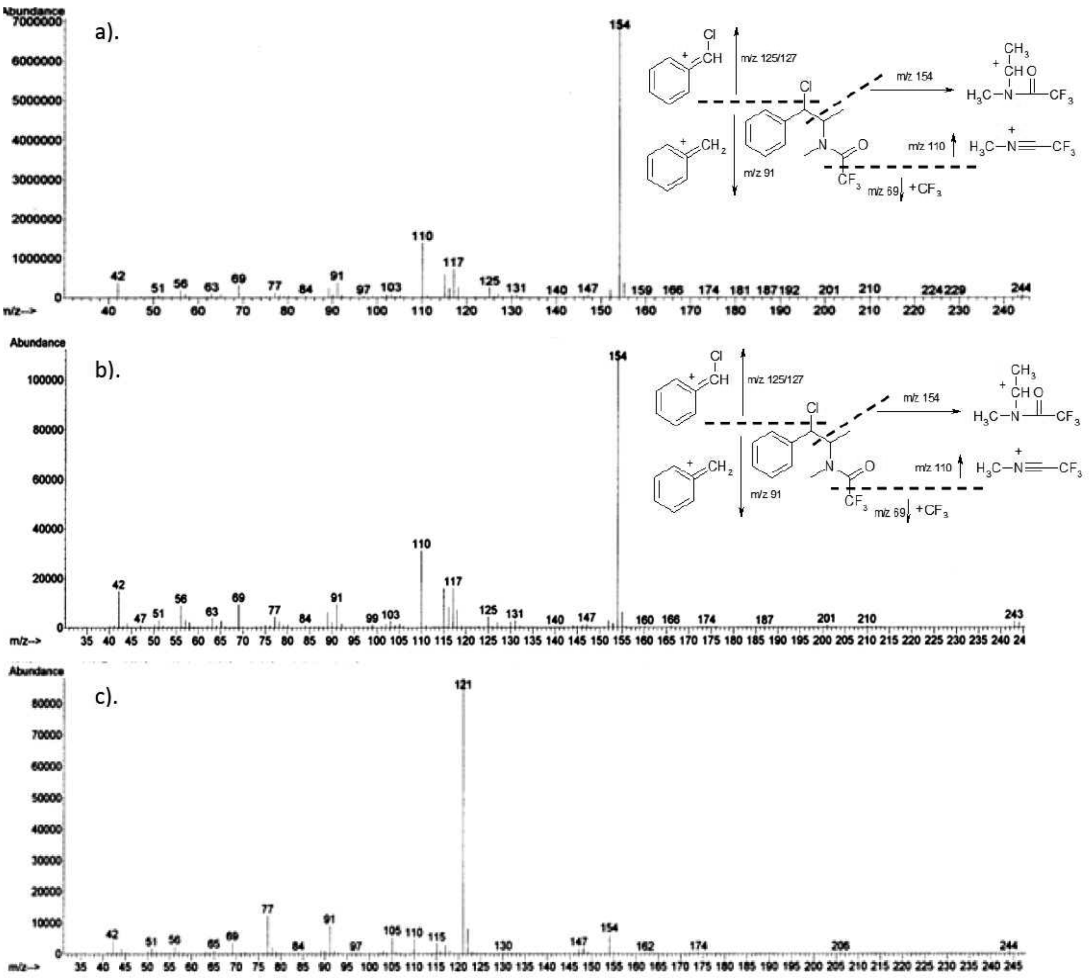

Figure 7. Mass spectra of compound determined in **2a**-TFAA. (a) (1*S*,2*S*)-(+)-Chloropseudoephedrine-TFAA. (b) (1*R*,2*R*)-(−)-Chloropseudoephedrine-TFAA. (c) Unidentified-TFAA.

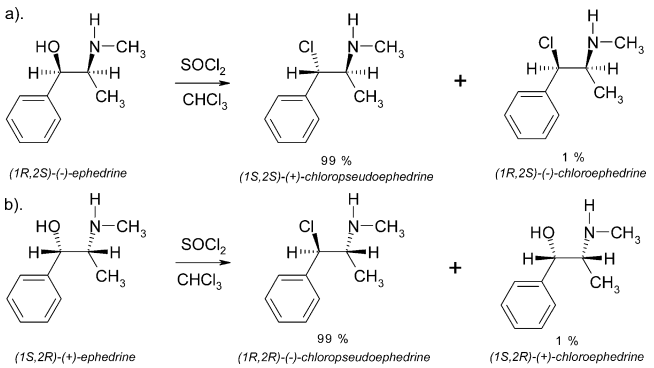

Figure 8. Reaction of (a) (1*R*,2*S*)-(−)-ephedrine and (b) (1*S*,2*R*)-(+)-ephedrine with thionyl chloride.

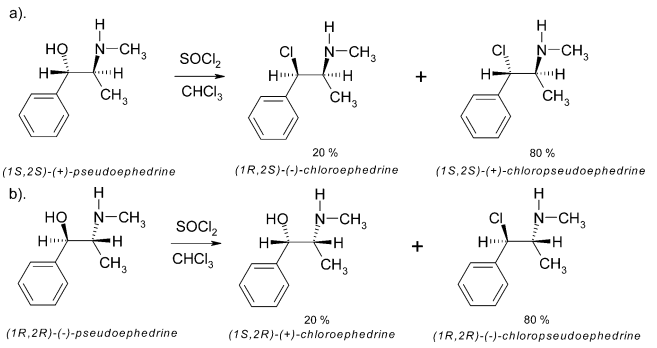

Figure 9. Reaction of (a) (1*S*,2*S*)-(+)-pseudoephedrine and (b) (1*R*,2*R*)-(−)-pseudoephedrine with thionyl chloride.

NMR spectroscopy is one of the most powerful non-destructive analytical techniques that provides direct information on the structure of compounds, but it is not as sensitive as the GC/MS technique, as can been seen with detection of the 1% diastereomeric impurity produced from ephedrine enantiomers by GC/MS. Because 2D NMR is needed to fully elucidate the stereoisomers, both techniques were necessary to determine chiral composition of synthesized samples. The combination of NMR and GC/MS should be considered as a suitable approach for chiral analysis of other compounds and useful for various fields which require accurate stereochemical data. The examples here are secondary amines required for forensic purposes, but can be equally applied to molecules of interest to pharmaceutical and general analytical science.

■ ASSOCIATED CONTENT

Supporting Information

Additional information as indicated in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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