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A STUDY OF IMPURITIES FOUND IN METHAMPHETAMINE SYNTHESIZED FROM EPHEDRINE

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Summary

The synthesis of methamphetamine from ephedrine via reduction with hydriodic acid is discussed. Impurities which arise from this method are identified and rationalized. The in situ formation of iodoephedrine from ephedrine leads to trace impurities via internal substitution to 1,2-dimethyl-3-phenylaziridine, followed by retro ring-opening and hydrolysis to phenyl-2-propanone (P-2-P). This ketone or the retro ring-opened aziridine further condenses in an aldol condensation followed by dehydration to give 1-benzyl-3-methylnaphthalene and 1,3-dimethyl-2-phenylnaphthalene. Two-dimensional nuclear magnetic resonance (2-D NMR) was utilized to elucidate the structure of these impurities.

Key words: Two-dimensional nuclear magnetic resonance; Methamphetamine; Ephedrine; Synthesis; By-products

Introduction

One of the most frequently abused drugs in the United States is methamphetamine (2), a stimulant popularly known as "crank" or "speed." That used in the illicit trade is synthesized in clandestine laboratories by a variety of routes and often contains impurities arising from incomplete reaction and inadequate purification of intermediates and/or the final product. Knowledge of these impurities is important for several reasons. It can provide useful intelligence concerning illicit production revealing information on the synthetic methods used to produce the drug, including necessary chemicals and equipment. Hence law enforcement officials can monitor the production and sale of commercially available precursors for methamphetamine and this can lead to the detection of clandestine laboratories. Secondly, interest in the presence or absence of specific impurities may lead to the identification of samples which are of a common origin, i.e. conspiracy links. A third area of interest in these impurities is in the potential harmful effects on methamphe-

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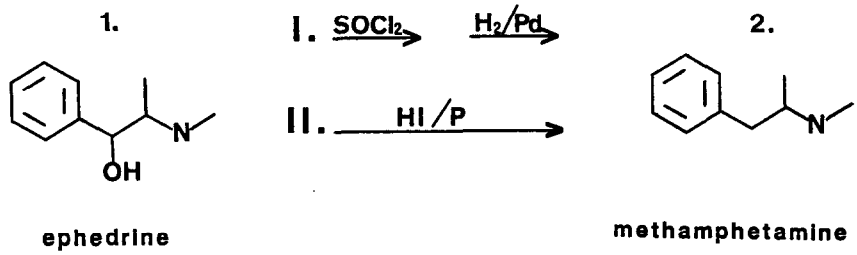

ephedrine methamphetamine

Fig. 1. Clandestine synthetic routes for (+)methamphetamine (2) via (−)ephedrine (1). Route I employs a two step reaction process, thionyl chloride ($SOCl_2$) followed by catalytic hydrogenation. Route II employs a one-pot reaction with hydriodic acid (HI) and red phosphorus.

tamine users i.e. recent (1984—1986) developments indicate that possible methamphetamine impurities are responsible for cases involving Huntington's Choreform movement [1]. Finally, impurities in methamphetamine are important to forensic chemists performing sample analysis due to possible interferences with the analytical technique being used.

Allen and Kiser considered the stereochemistry, mechanism and by-products which result from the conversion of ephedrine to methamphetamine [2]. In that process, ephedrine is converted to its chloro analog followed by catalytic reduction to methamphetamine, Fig. 1 (route I). In the present article, we discuss the conversion of ephedrine (1) to methamphetamine (2) via hydriodic acid reduction (route II). The chemistry involved in route II was advanced by information gathered from Allen and Kiser's article.

Illustration of the commonality of these syntheses is seen in the following facts. Stereochemistry implicit in the first route I also applies with hydriodic acid/red phosphorus reduction. That is, only (−)ephedrine and (+)-pseudoephedrine yield (+)methamphetamine. Furthermore, the intermediate in route I (chloroephedrine from ephedrine with thionyl chloride) is a halo analog, and such is the case in route II. Ephedrine reacted with HI initially creates iodoephedrine in situ. Finally, the by-products of aziridines are common to both synthetic routes.

Interestingly, there are significant mechanistic and by-product differences between these two routes, primarily due to the heated protic acid medium of the latter (route II) versus the ambient aprotic medium of the former (route I) which make further rearrangements in route II unique.

Chemistry

When ephedrine (1) is heated with hydriodic acid, with red phosphorus (Caution, Ref. 3) or without, initially the hydroxyl is replaced with iodine (Fig. 2, compound 3). It is from this point that the rearrangement chemistry of trace impurities starts. The halo compound is subject to reduction in the hydriodic acid medium leading to the target compound (2),

(+)methamphetamine [4]. Hydrogen iodide dissociates at higher temperatures to iodine and hydrogen, which effects hydrogenations. The reaction is reversible. Its equilibrium is shifted in favor of the decomposition by the reaction of hydrogen with organic compounds (iodoephedrine in this case) in the reduction, but it can also be affected by removal of iodine. This can be accomplished by allowing iodine to react with phosphorus to form phosphorus triiodide which decomposes in the presence of water to phosphorous acid and hydrogen iodide. In this way, by adding phosphorus to the

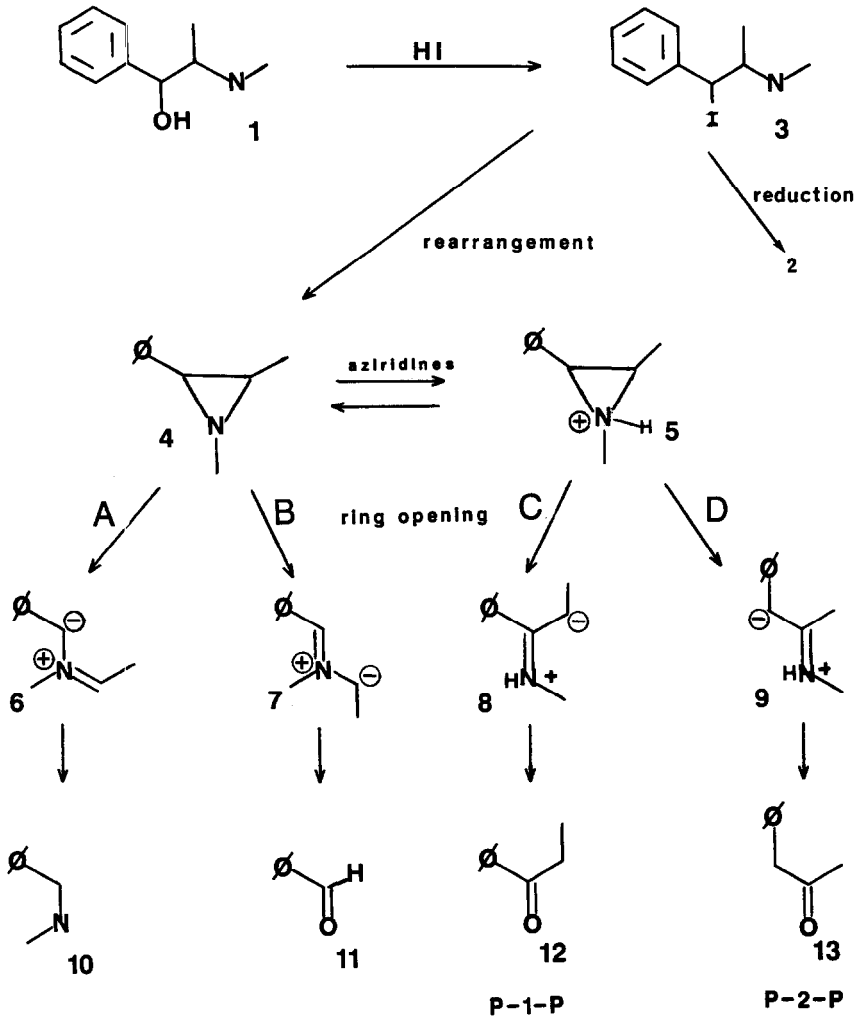

Fig. 2. Reaction of ephedrine (1) with hydriodic acid (HI) initially produces iodoephedrine (3). The in situ reduction of 3 yields 2. Internal substitution of 3 produces 1,2-dimethyl-3-phenylaziridines (4). Retro ring-opening followed by hydrolysis of 5 produces phenyl-2-propanone (13).

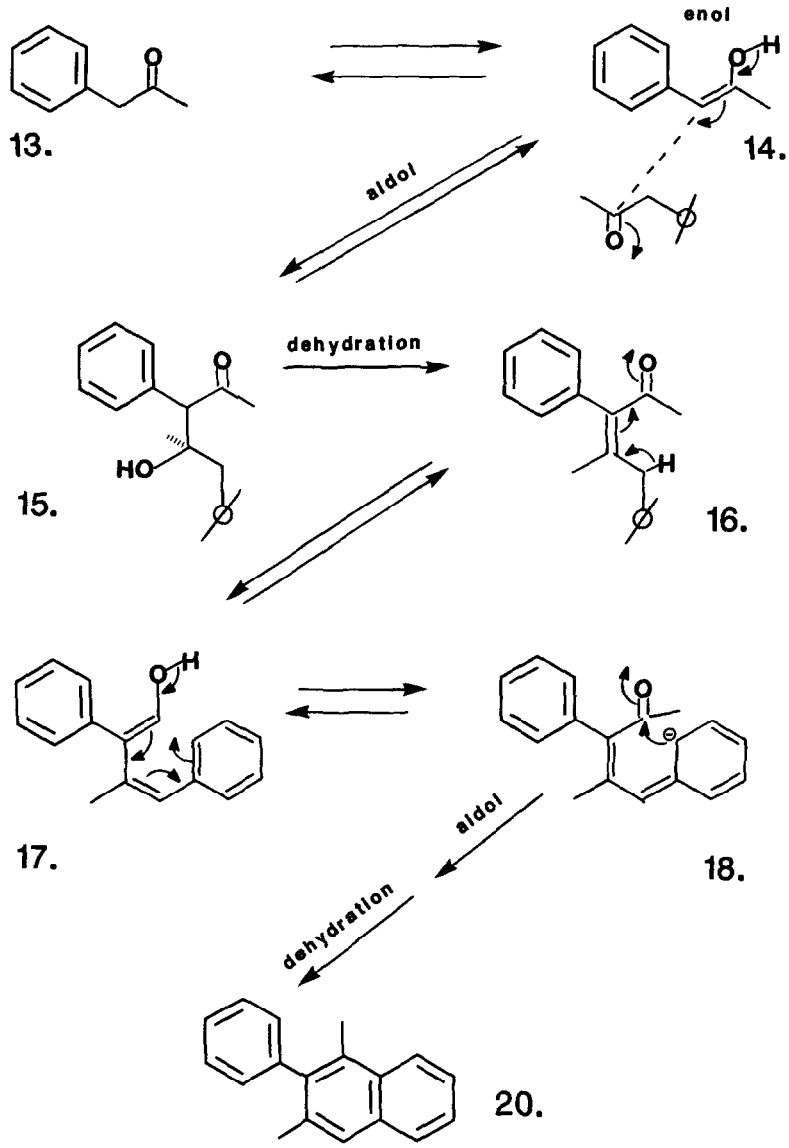

Fig. 3. Mechanistic rationalization for the aldol condensation of 1,3-dimethyl-2-phenylnaphthalene (20) from phenyl-2-propanone (13) in acid.

reaction mixture, hydrogen iodide is recycled and the reducing efficiency of hydriodic acid is enhanced [5].

The halo compound may undergo an internal substitution reaction, whereby nitrogen replaces iodine, leading to routes A, B, C and D (Fig. 2). Due to the extreme acidity of the reaction mixture, only routes C and D are

viable considerations. The protonated nitrogen of the aziridine controls retro ring-opening to produce the zwitterion intermediates 8 or 9. The rational choice of route D, based on the highly favored zwitterion intermediate 9 with resonance overlap to the aromatic ring, is borne out with experimental fact. The product of retro ring-opening, followed by hydrolysis of 1,2-dimethyl-3-phenyl-aziridine (4 or 5) is P-2-P (13) [6]. Thus, P-2-P is a common impurity in these clandestine laboratory preparations of (+)methamphetamine. This anomaly has puzzled a number of forensic investigators where the clandestine synthesis was known to start from ephedrine and not the popular route P-2-P/methylamine/Schiff base reduction via aluminium foil.

From the selected number of clandestine methamphetamine samples screened for the presence of trace impurities, we have found that the major portion of P-2-P produced in this reaction undergoes self-condensation (aldol) to afford hydrocarbon impurities. These impurities are 1-benzyl-3-methylnaphthalene (19) and 1,3-dimethyl-2-phenylnaphthalene (20). Both compounds 19 and 20, incorporate two molecules of P-2-P as result of an aldol condensation, followed by dehydration, followed by a second internal condensation and dehydration. Figure 3 illustrates a mechanistic interpertation outlined for the production of 20. A similar construction may be outlined for compound 19.

It should be noted that the mechanistic interpretation outlined in Fig. 3 is only speculative. This is due, in part, to the transient nature of compounds 4–9 and 15–18. However, separate reflux reaction of P-2-P (13) with hydriodic acid produced compounds 19 and 20 in moderate yields. Additionally, it should be clear that any alternative route which accounts for condensation to 19 and 20 must disrupt, at some point, conjugation of the aromatic ring as in structures 18. Furthermore, since the ring-opened compound 9 is in itself a masked ketone, its participation in the condensation reactions to 19 and 20 is reasonable.

Experimental

Isolation of impurities

Impurities from clandestine (+)methamphetamine samples prepared from ephedrine according to synthetic route II (Fig. 1), were isolated by trituration of 1-g quantities of illicit material with 5 ml of acetone. After filtration, the acetone was evaporated and residues partitioned between 0.1 N H_2SO_4 and 0.5 ml of dichloromethane. Alternatively, the neutral impurities contained in the dichloromethane may be removed from the acetone evaporated residues by triturating with diethyl ether. Introduction of these neutral impurities into a MS via GC resulted in data presented in Figs. 4 and 5. Materials (compounds 19 and 20) used for identification via NMR were obtained by refluxing P-2-P with hydriodic acid. Isolation of compounds 19, and 20 was achieved by removal of excess P-2-P by the use of the sodium

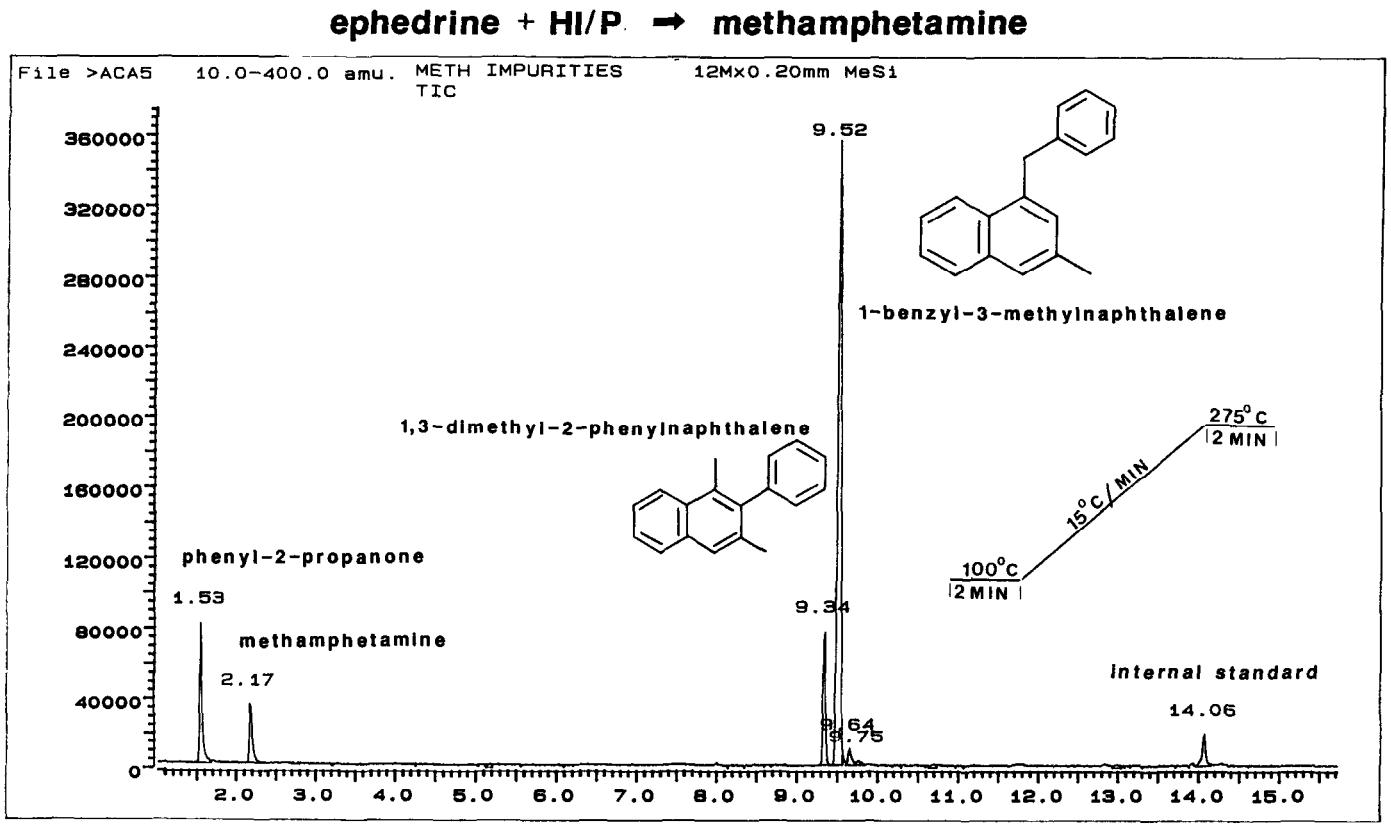

Fig. 4. Total ion chromatograph (TIC) of trace impurities produced from ephedrine/hydriodic acid/red phosphorus reaction. Chromatography achieved on a fused silica capillary, bonded methyl silicone, 12 m × 0.2 mm column, temperature ramp as illustrated, internal standard *n*-octacosane.

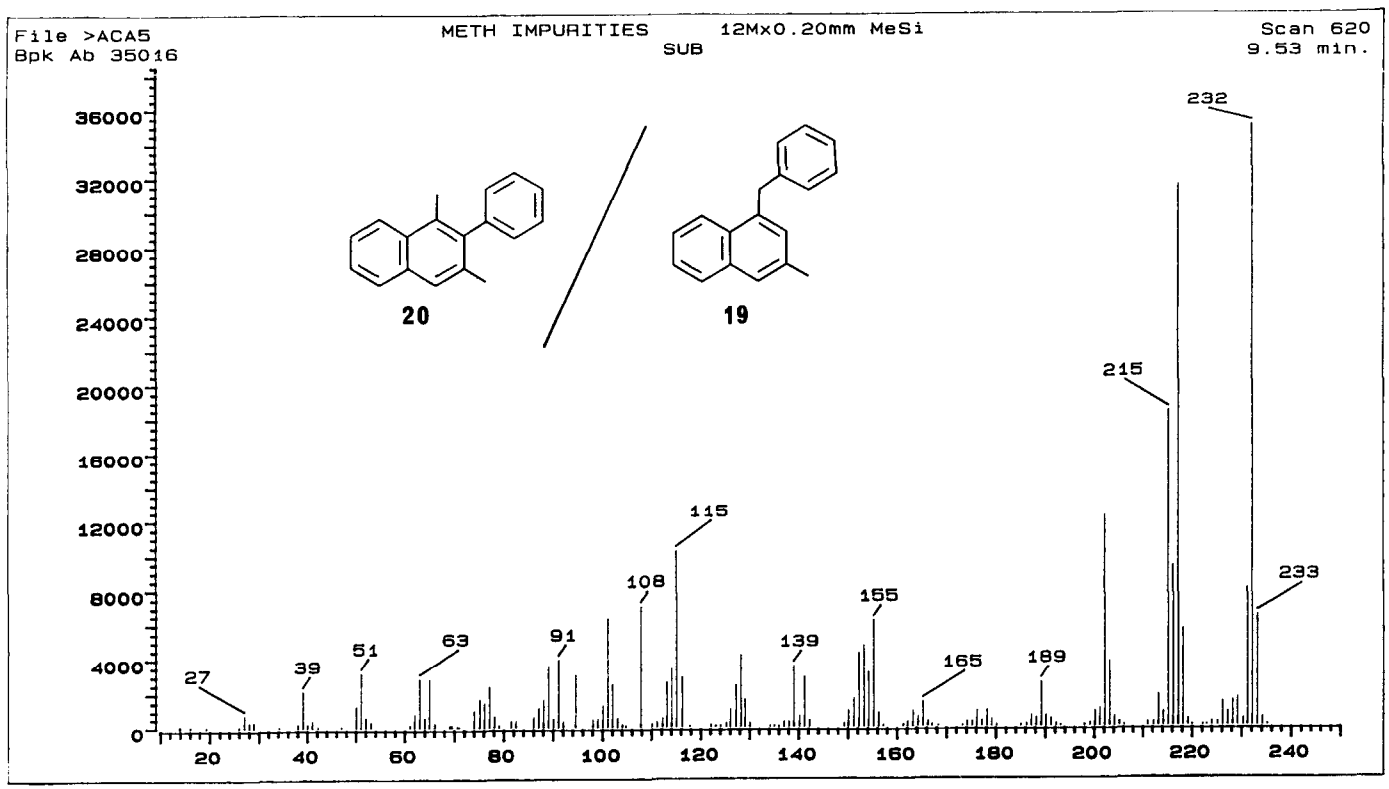

Fig. 5. Electron impact mass spectrum of 1-benzyl-3-methyl naphthalene (19) or 1,3-dimethyl-2-phenylnaphthalene (20) obtained at 70 eV with 200 °C source temperature.

bisulfite addition product. Further separation of compound 19 from 20 was effected through neutral alumina column chromatography. Compound 19 proved to be more slowly eluted than compound 20. Data (MS, ^{1}H NMR, IR, UV, and GC) for 19 and 20 obtained from refluxing P-2-P with hydriodic acid were identical to those obtained from preparing methamphetamine from ephedrine with hydriodic acid and from clandestine (+)methamphetamine sample known to be synthesized from (−)ephedrine and hydriodic acid.

Instrumentation

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were obtained on General Electric QE−300 and GN−500 (Fremont, California) spectrometers. Spectral collections on the titled compounds were collected on 0.5 molar solutions in $CDCl_3$. Characterizations were based on information obtained from proton-proton, proton-carbon, relayed proton-carbon and long range proton-carbon cross correlation-two dimensional (2-D) experiments.

Gas chromatography/mass spectrometry was performed on a Hewlett-Packard 5987a GC/MS system, interfaced with a 5880a series GC. The gas chromatograph was operated in the split mode (50:1) and was equipped with a 12 m × 0.20 mm i.d. fused silica capillary column bonded methyl silicon liquid phase. Injector temperature was maintained at 260 °C. Oven temperature was programmed as follows: initial temperature, 100 °C; initial hold, 2 min; temperature program rate, 15 °C/min; final temperature, 275 °C; final hold, 2 min. Ion source was maintained at 200 °C under electron impact conditions at 70 eV. Helium was used as carrier gas at a flow rate of 50 cm/s.

Results and Discussion

Gas chromatography-mass spectral data were obtained on impurities 19 and 20. Figure 4 represents the reconstructed electron impact mass spectral ion chromatograph for trace impurities isolated from (+)methamphetamine prepared from ephedrine using hydriodic acid and red phosphorus. The virtually identical electron impact mass spectra of 19 and 20 justifies illustration of both compounds together in Fig. 5. Accurate mass measurements allowed the computation of the empirical formula as $C_{18}H_{26}$. Notwithstanding the power of mass spectral information, these compounds along with many of the "controlled substance analogs" (Designer Drugs) available on the illicit market are not within reach of structural elucidation via mass spectrometry. Since a number of substituted naphthalenes, as well as indenes, fit the available data, we turned to NMR for the structural elucidation.

A technique which is now reducing such structural elucidation problems to routine is two-dimensional nuclear magnetic resonance spectroscopy (2-D NMR), which provides a wealth of information regarding connectivity and conformational aspects of molecular structure. In a two-dimensional NMR

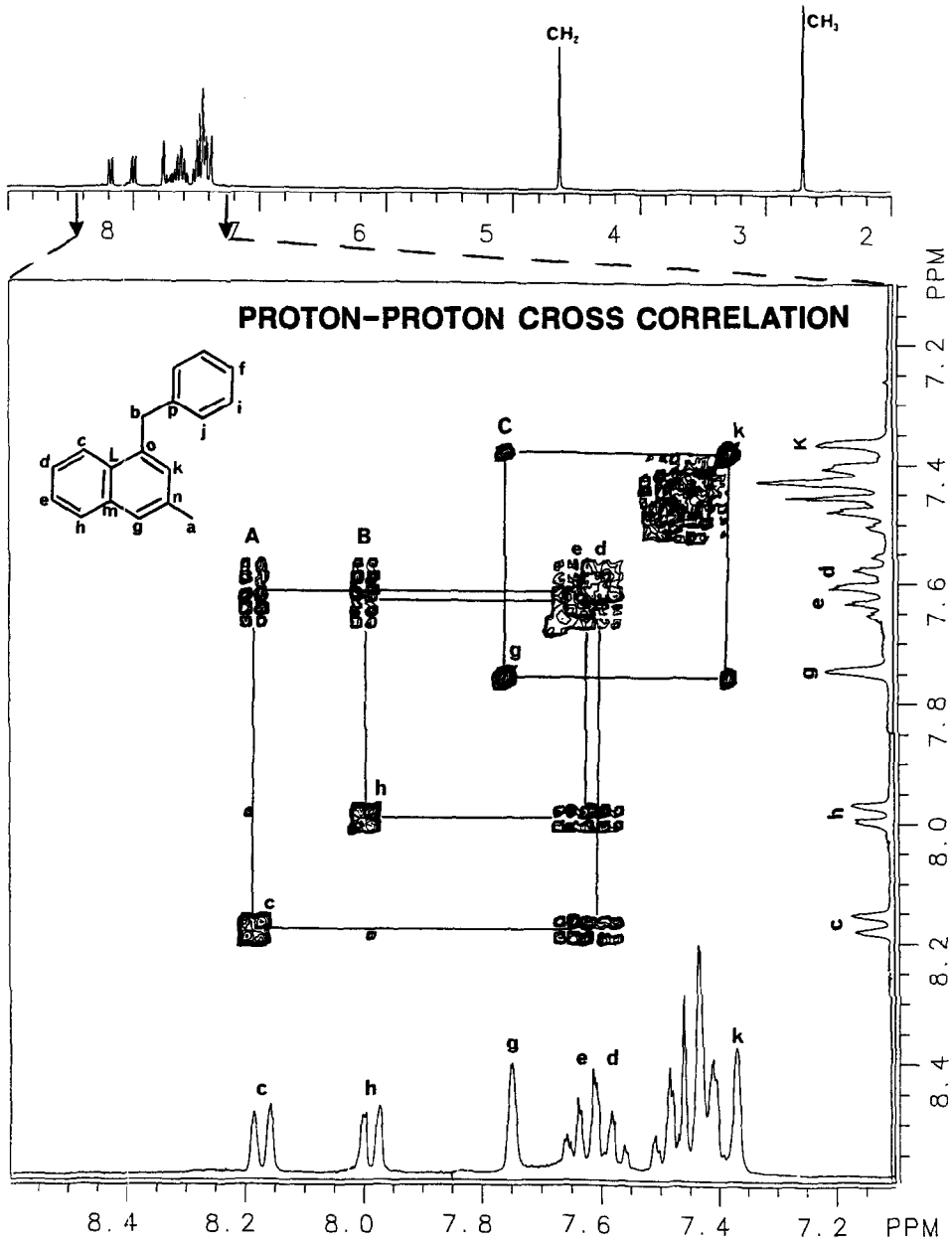

Fig. 6. Proton-proton cross correlation on 0.5 molar 1-benzyl-3-methylnaphthalene (19) obtained at 300 MHz with 128 blocks of sixteen acquisitions, recycle time 0.97 s, total time 30 min. Horizontal, vertical and diagonal resonances represent the aromatic region 7.1–8.5 ppm (b). Contour cross peaks A (coupling *c*, *e* and *d*), B (coupling *h*, *e* and *d*) and C (coupling *g* and *h*) illustrate couplings.

experiment, data are collected as a function of two independent time variables, termed the evolution period and the signal acquisition period. The amplitude and phase of signals during the detection period is influenced by events experienced by the spins during the evolution period [7–10; also, Jener, Ampere International Summer School, Yugoslavia, 1971; unpublished]. Repetition of the experiment with variable evolution periods enable the frequencies prevailing during the evolution period to be characterized. A double Fourier transformation is then performed on these time domain data and the resulting two-dimensional spectrum is a display of intensity as a function of two independent frequencies. Several excellent reviews and monographs on two-dimensional experiments are available [10–15].

Proton-proton cross correlation

Homonuclear shift correlation spectroscopy (COSY) experiment, one of the first 2-D experiments to be proposed [6], correlates chemical shifts of scalar coupled nuclei of identical type [9,17,18; also Jeener, Ampere International Summer School, Yugoslavia 1971, unpublished]. The COSY spectrum of 1-benzyl-3-methylnaphthalene (19) is shown in Fig. 6b in contour display mode. The trace shown at the bottom of the 2-D spectrum is the normal proton spectrum. Proton frequencies are displayed along both dimensions, with peaks along the 'diagonal' resembling the normal spectrum. The 2-D spectrum is symmetric about the diagonal. Peaks away from the diagonal, termed cross peaks, are the ones of interest, e.g. the group of peaks labeled A arise from spin-spin coupling between proton c and protons d and e. Similarly, coupling between proton h and protons e and d gives rise to the group of peaks labeled B. This pattern is characteristic of a substituted naphthalene system. Protons k and g give rise to broad singlets and are mutually coupled as evidenced by cross peak C between them. Cross peaks between protons f, i, and j suggest another isolated phenyl system in the molecule. Inspection of the normal proton and carbon spectra (Figs. 6 and 7) suggest the presence of a methylene and a mehyl group isolated from other protons.

Carbon-proton cross correlation

Information about heteronuclear connectivity can be obtained from a heteronuclear chemical shift correlation experiment [10–13]. Carbon-proton shift correlation 2-D spectrum of (19) is shown in Fig. 7. The horizontal dimension (f1 axis) represents proton chemical shifts, and carbon chemical shifts are displayed along the vertical dimension (f2 axis). Normal carbon and proton spectra are plotted along respective dimensions for reference. Presence of a peak in the 2-D heteronuclear chemical shift correlation indicates direct bonding between a particular carbon and its related proton(s). As an example, the correlation peak labeled aa indicates direct bonding between the methyl carbon at 21.6 ppm and the methyl protons at 2.7 ppm. The peak labeled bb correlates the methylene carbon to the methylene protons. Peaks in the aromatic region (see insert in Fig. 7) determine assignments of carbon

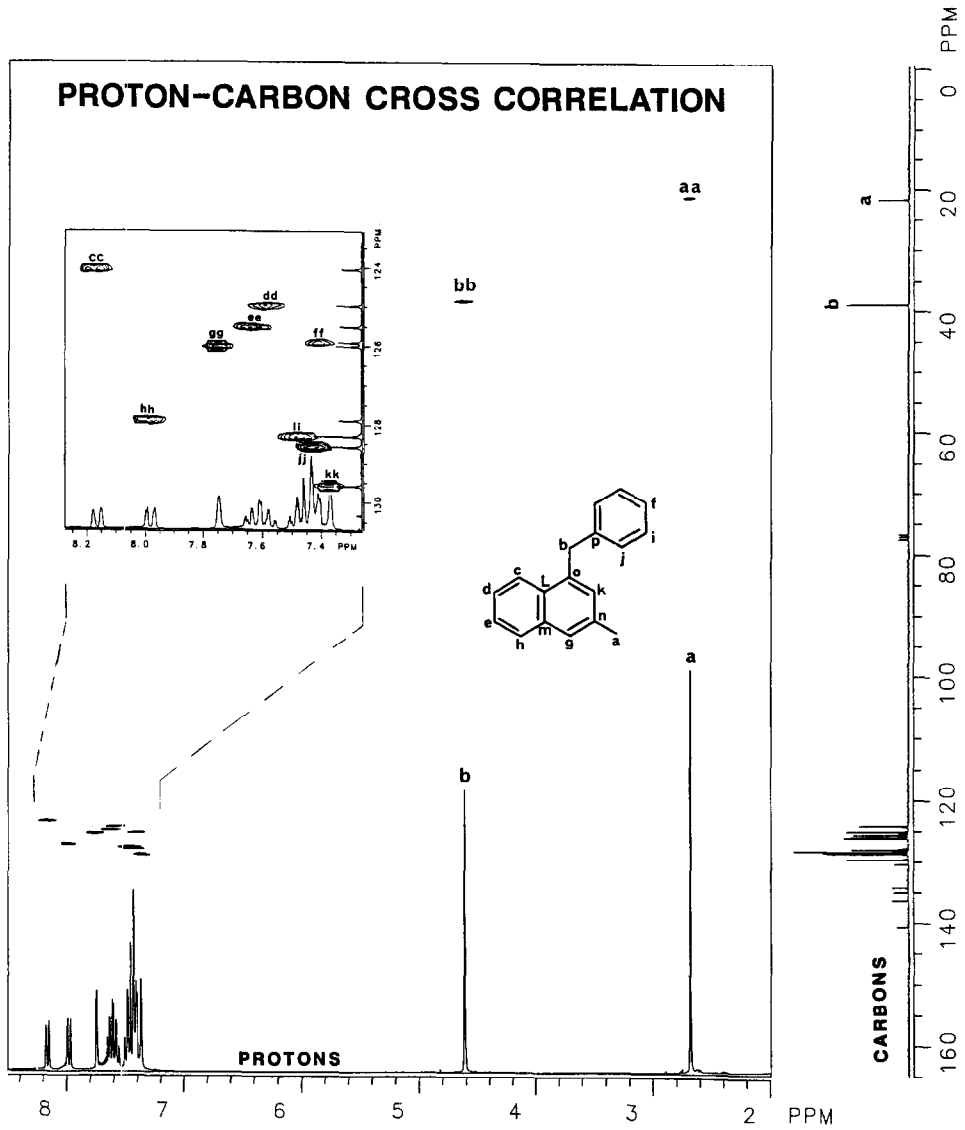

Fig. 7. Proton-carbon cross correlation on 0.5 molar 1-benzyl-3-methylnaphthalene (19) obtained at 300 MHz with 256 blocks of 8 acquisitions, recycle time 0.8 sec, total time 30 min. Horizontal (proton) and vertical (carbon) resonances are cross correlated (contour lines), i.e. *bb*, methylene protons, 4.6 ppm and methylene carbon, 40 ppm.

peaks when proton assignments are known and vice versa. Since only protonated carbons can give rise to correlation peaks in this 2-D spectrum, this directly bonded correlation experiment does not yield any information on other non-protonated carbon sites.

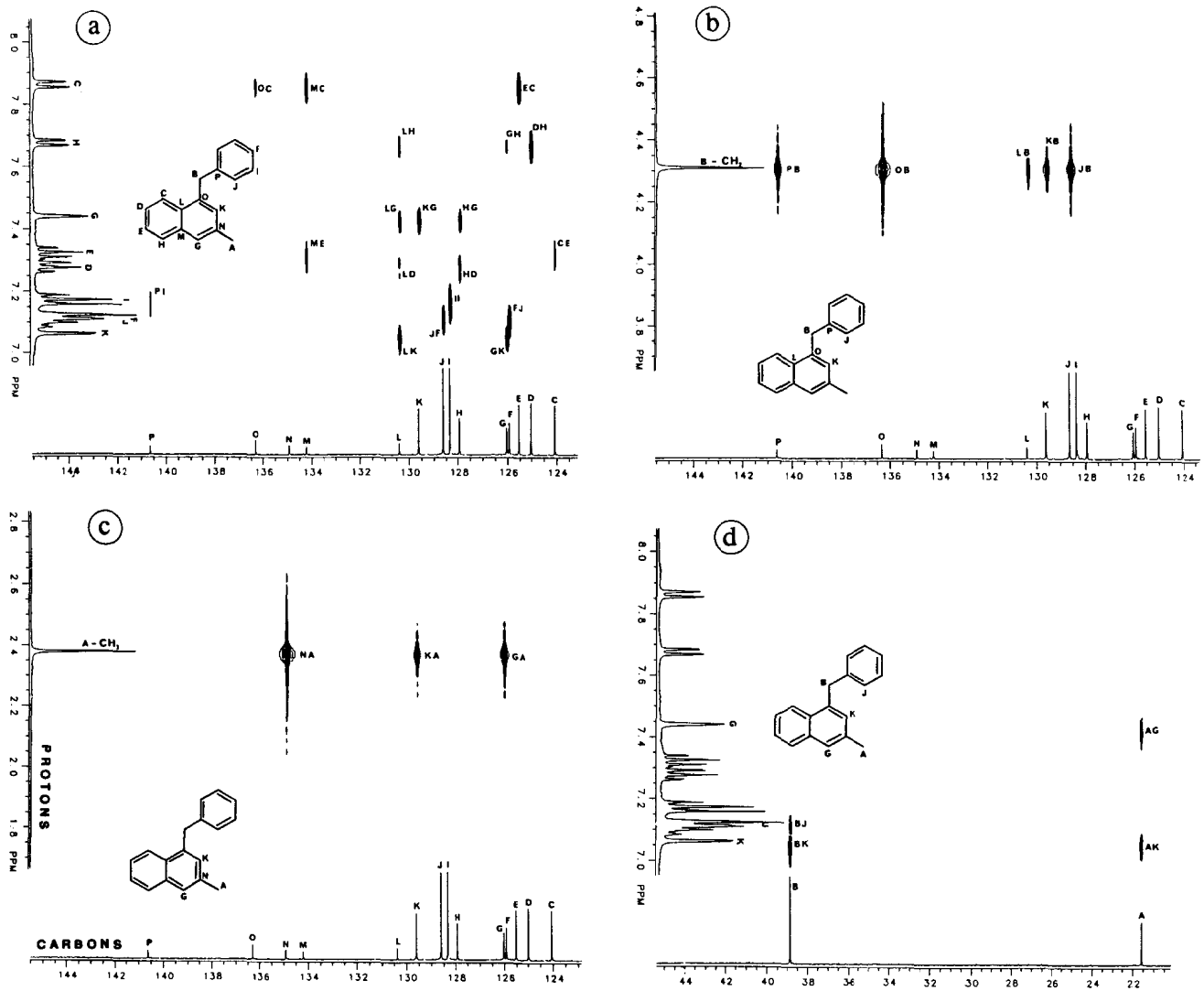

Fig. 8. Long-range proton-carbon cross correlation (two and three bond coupling) on 0.5 molar 1-benzyl-3-methyl-naphthalene (19) obtained at 500 MHz with 128 blocks of 256 acquisitions, recycle time 0.8 s, total time 9 h. Horizontal (carbon) and vertical (proton) resonances are long-range cross correlated via contour lines, i.e. the methyl carbon resonance at a 21.6 ppm is coupled to proton resonances G, 7.44 ppm and K, 7.06 ppm (d).

Long range proton-carbon cross correlation

Information regarding connectivity patterns of non-protonated carbons can be obtained from a long-range proton-carbon correlation experiment, which correlates carbon and proton chemical shifts on the basis of small long-range couplings [17—21]. Non-protonated carbon connectivity information can also be obtained from the carbon-carbon double quantum experiment (Inadequate), however the long-range experiment provides *significantly better sensitivity.* Long-range carbon-proton, two or three bond, couplings typically range from 0—10 Hz. Expanded plots of the 2-D long-range carbon-proton experiment for 19 are shown in Fig. 8a—d along with the corresponding carbon and proton reference spectra. The long-range correlation spectra also shows some weak peaks due to "leakage" from the directly bonded connectivities. However, these can be differentiated easily through a comparison with the directly bonded correlation spectrum, Fig. 7. One of the foremost advantages of long-range correlation spectra is information about non-protonated carbons, which is clearly evident in Figs. 8a, 8b and 8c. these spectra show five non-protonated carbon sites (L, M, N, O, and P) with long-range coupling to various protons. Important connectivities substantiating the presence of a benzyl CH_2 group are labeled PB, OB, LB, KB and JB; (Fig. 8b) which are correlations between the methylene protons B and five aromatic carbons which are two or three bonds away (Fig. 8b). Similar evidence can be found in Figs. 8c and 8d for long-range connectivities of the methyl protons and three aromatic carbons, G, K and N. Connectivities AK and BK (Fig. 8d) show that the methyl carbon A and methylene carbon B are long-range coupled to proton K. Peaks KA (Fig. 8c) and KB (Fig. 8b) show long-range coupling of carbon K to the methyl protons A and methylene protons B, respectively. This established the locations of the benzyl and methyl groups at the 1 and 3 position, respectively of the naphthalene ring.

Relayed carbon-proton cross correlation

Another technique for assignment of neighboring carbons is heteronuclear relay which relies on spin coupling between a directly bonded proton and a remote proton (31—35). Here, connectivity between a directly bonded proton and a remote proton is established first by a homonucler magnetization transfer step, and is then conveyed to the attached carbon using a heteronuclear magnetization transfer step. The 2-D spectrum then displays correlation of a carbon site and a remote proton, as well as that of directly bonded protons. Partial plot of a 2-D relay spectrum for 19 is shown in Fig. 9, with carbon chemical shifts along the f2 dimension and proton shifts along f1 dimension. The intense peak, labeled CC shows the direct correlation between carbon C and proton C. On scanning through the proton dimension, the relay peak labeled D—CC, of carbon C to neighboring proton D, can be seen. For carbon D the direct peak DD, as well as the relay peaks (C—DD and E—DD) to proton C and proton E can be seen. Following the relay to carbon E, the relayed peaks (D—EE and H—EE) to proton D and proton H

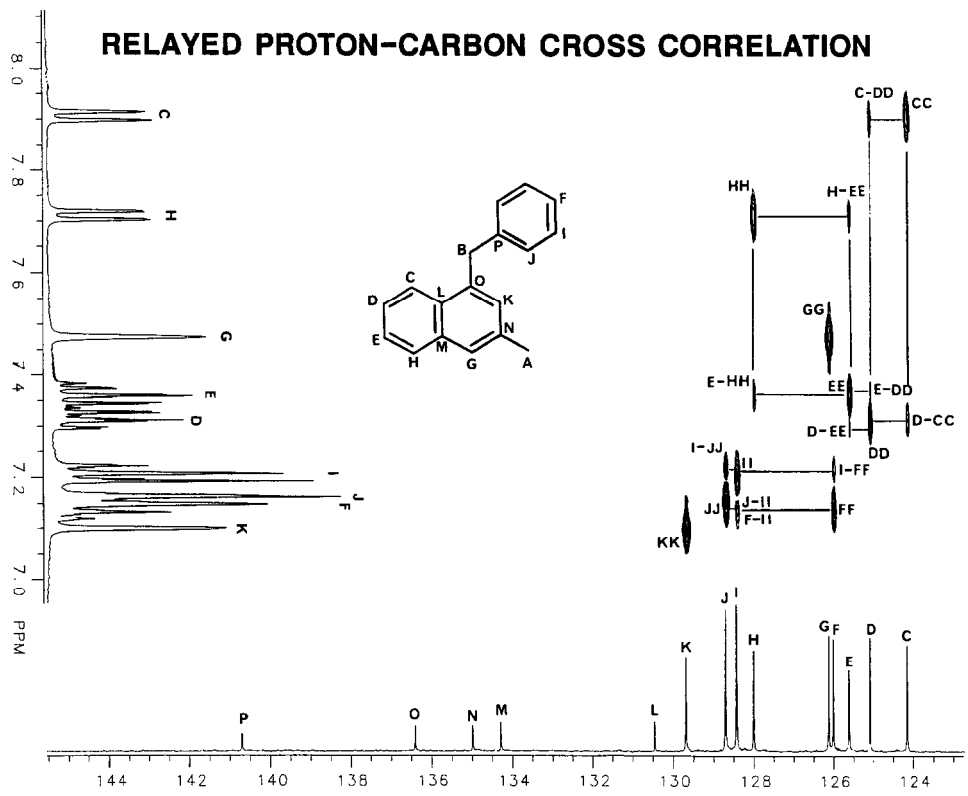

Fig. 9. Relayed proton-carbon cross correlation on 0.5 molar 1-benzyl-3-methylnaphthalene (19) obtained at 500 MHz with 182 blocks of 16 acquisitions, recycle time 1.1 s, total time 75 min. Relayed resonances, contour lines C—DD, D—CC, E—DD, D—EE, E—HH and H—EE are connectivities between direct peaks CC, DD, EE and HH.

are visible. From carbon H, the relay (E—HH) leads back to proton E. The relayed magnetization transfer terminates when non-protonated carbons L and M are encountered. Relay patterns can also be established for carbons I, J, and F. Since relay experiments depend on direct bonding for magnetization transfer to the carbon, it cannot be used to establish connectivities to non-protonated carbon sites.

Conclusion

(+)Methamphetamine synthesized from (−)ephedrine or (+)-pseudoephedrine via hydriodic acid (route II, Fig. 1), has been investigated. Impurities of iodoephedrine (3), 1,2-dimethyl-3-phenylaziridine (4) and P-2-P (13) have been observed (detection as outline in reference 1). Impurities of 1-benzyl-3-methylnaphthalene (19) and 1,3-dimethyl-2-phenyl-naphthalene (20)

have been isolated (see Experimental and Figs. 4 and 5) and their structures elucidated via NMR experiments (Figs. 6–9). The presentation of spectral data on 20 has been omitted for economy of space.

Since compounds 19 and 20 are, each, the product of two molecules of P-2-P condensing in acidic medium, the presence of impurities may be used to distinguish the synthetic route of hydriodic acid (Fig. 1, route II) from the catalytic reduction method (Fig. 1, route I) in clandestine (+)-methamphetamine samples.

The utility of 2-D NMR has been highlighted through the structural elucidation of compound 19 (Figs. 6–9). Since this problem, along with similar ones in the area of Designer Drugs, would have been virtually impossible to solve by mass spectrometry and IR, it seems that the use of NMR spectroscopy will certainly grow within the forensic community.

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