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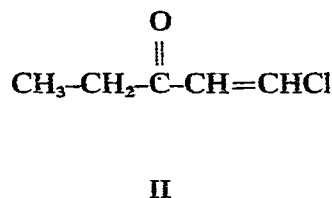
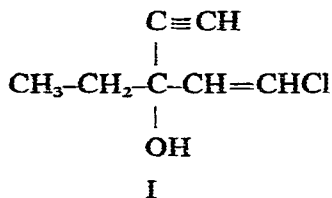
The analysis of impurities in ethchlorvynol by gas chromatography-mass spectrometry

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Ethchlorvynol (1-chloro-3-ethyl-1-penten-4-yn-3-ol; I) is a widely used synthetic sedative. The reports of ethchlorvynol abuse resulting in intoxication, addiction, or death have been well documented¹⁻³. In our work it was noticed that a pure sample of ethchlorvynol (Placidyl¹) gave many peaks by gas-liquid chromatography. This led us to believe that many impurities may be present in the commercial product as well as in the sample supplied by Abbott.



Ethchlorvynol exerts its action on the central nervous system and the extent of depression can be altered by these impurities. For this reason it is imperative that the impurities be identified. Various methods^{1,4-8} have been described for determining ethchlorvynol in biological specimens. Washburn and co-workers^{9,10} reported ethchlorvynol ketone (1-chloro-1-penten-3-one) (II) in 0.1% concentration as an impurity in the pharmaceutical preparation.

The purpose of this paper is to identify other impurities by means of gas chromatography-mass spectrometry (GC-MS).

EXPERIMENTAL

Several 500-mg capsules of Placidyl (Abbott, Chicago, Ill., U.S.A., Lot Nos. 854-1499 and 43-320-AF) and a 5-g sample of ethchlorvynol were obtained. The samples were analyzed directly. The mass spectra were taken on a Finnigan Model 3200 gas chromatograph-mass spectrometer which was coupled to a Finnigan Model 6100 data system. The samples were chromatographed through a 5 ft. × 2 mm glass column, packed with 3% OV-17 on Gas Chrom Q, 80-100 mesh. A column temperature of 90° and a helium flow-rate of 20 ml/min were used. The electron impact (EI) mass spectra were obtained at 70 eV with the ion source set at 180°.

For the chemical-ionization (CI) mass spectra methane was used as the reactant gas with a source pressure of 1 torr. The emission was 1 MAMP power voltage was 2 V, and the source temperature was 120°.

RESULTS AND DISCUSSION

The gas chromatograms and gas chromatograms-mass spectra were similar for both the capsule obtained and the sample supplied by Abbott. The major compound I as well as small amounts of 1-chloro-3-methyl-1-penten-4-yn-3-ol (II), 1-chloro-3-

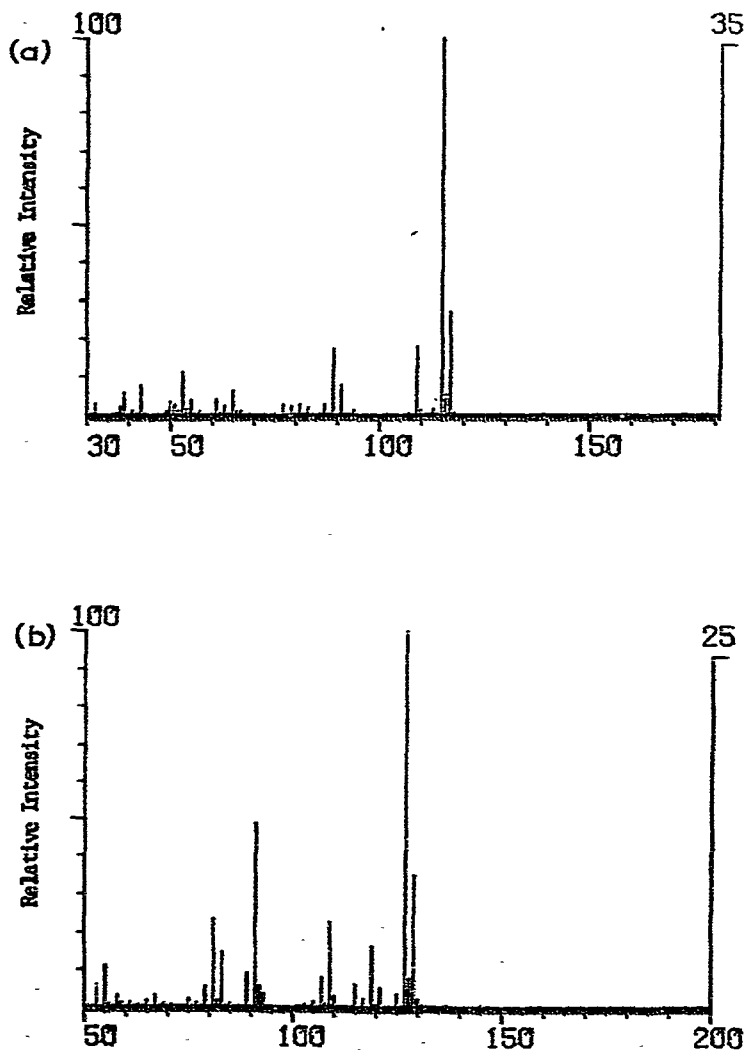


Fig. 1. Mass spectra of ethchlorvynol (I) by (a) EI and (b) CI.

propyl-1-penten-4-yn-3-ol (IV), and 3-pentanone (V) were found in both the capsule and vial. In addition the capsule contained a small amount of either 1,1- or 1,2-dichloro-3-ethyl-1-penten-4-yn-3-ol (VI).

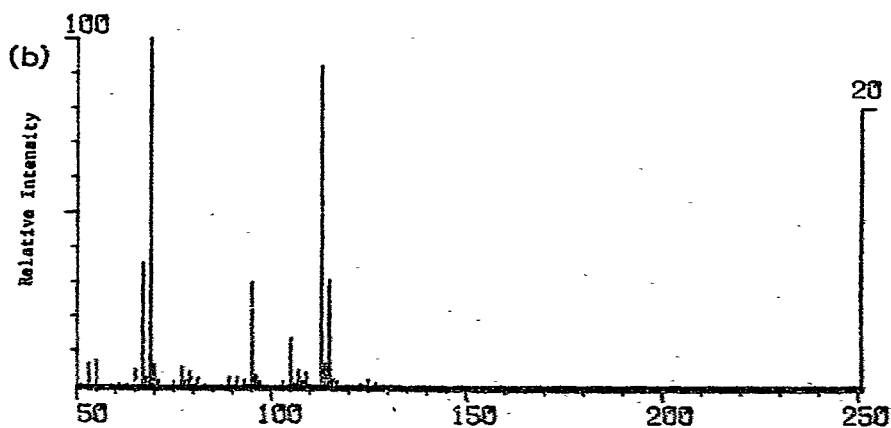
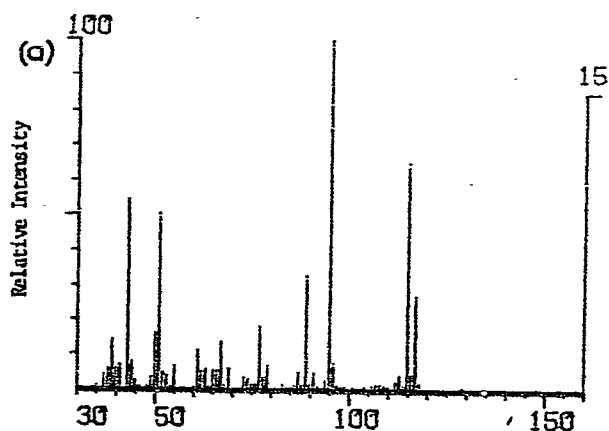
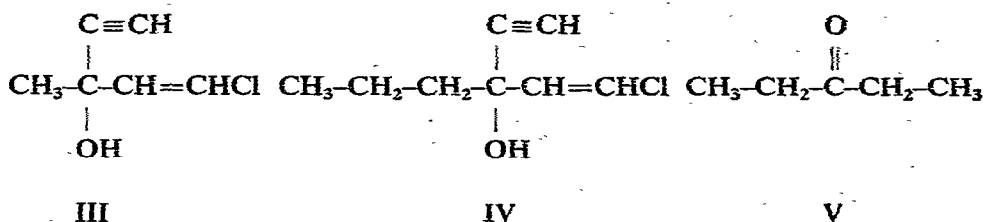
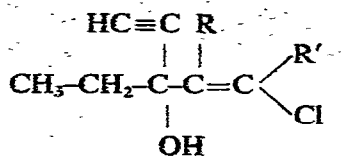


Fig. 2. Mass spectra of III by (a) EI and (b) CI.



VI $\text{R} = \text{H}, \text{R}' = \text{Cl}$ or $\text{R} = \text{Cl}, \text{R}' = \text{H}$

The mass spectra of I, III, IV, V, and VI are shown in Figs. 1-5. The analysis of the various alcohols present as impurities is summarized in Table I. The EI mass spectrum of ethchlorvynol agrees very closely with that reported by Fales *et al.*¹¹. The alcohols did not show prominent parent ions by EI. With the exception of III, the major route of decomposition was the loss of the alkyl portion of the molecule. The methyl derivative III showed loss of chlorine from the parent ion as the major route,

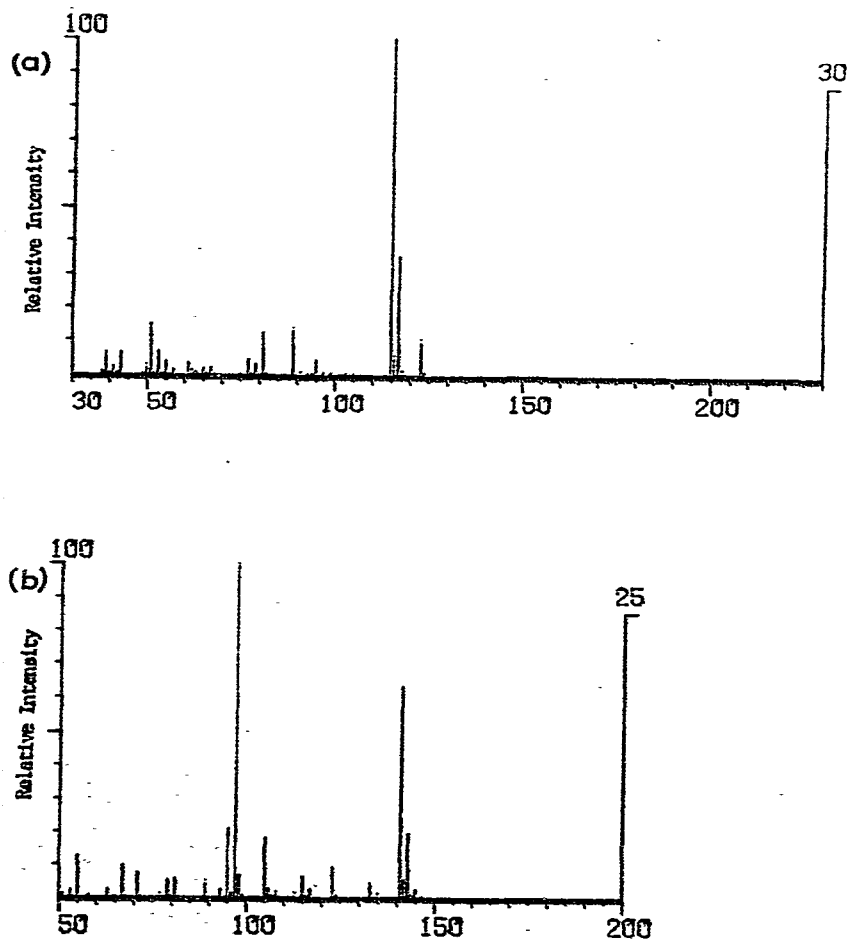


Fig. 3. Mass spectra of isomers of IV by (a) EI and (b) CI.

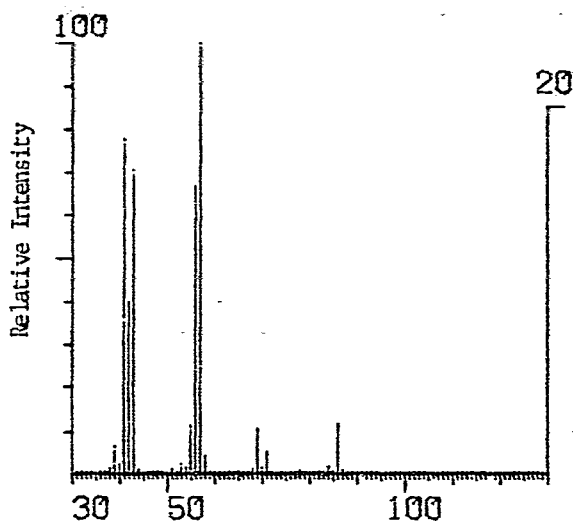


Fig. 4. Mass spectrum of V by EI.

TABLE I

FRAGMENTATION PATTERNS OF THE VARIOUS ALCOHOLS IN ETHCHLORVYNOL PREPARATION

| Compound | EI | | | | CI | |
|----------|------------------------------|------------|-------------------------------------|-------------------------------------|------------|---------------------------------|
| | Fragment cleaved from parent | Peak (m/e) | Intensity relative to base peak | M or M+1 - fragment | Peak (m/e) | Intensity relative to base peak |
| I | alkyl | 115 | 100 | (M+1) - water | 127 | 100 |
| | alkyl | 117 | 27 | (M+1) - water | 129 | 35 |
| | chlorine | 109 | 18 | M - chlorine - water | 91 | 48 |
| III | alkyl | 115 | 65 | (M+1) - water | 113 | 92 |
| | alkyl | 117 | 27 | (M+1) - water | 115 | 30 |
| | chlorine | 95 | 100 | (M+1) - chlorine | 95 | 30 |
| | | | | M - alkenyl chlorine | 69 | 100 |
| IV | alkyl | 115 | 100 | (M+1) - water | 141 | 64 |
| | alkyl | 117 | 37 | (M+1) - water | 143 | 22 |
| | chlorine | 123 | 12 | M - water - chlorine | 105 | 19 |
| | | | | M - alkenyl chlorine | 97 | 100 |
| VI | alkyl | 149 | 100 | (M+1) - water | 161 | 88 |
| | alkyl | 151 | 77 | (M+1) - water | 163 | 54 |
| | alkyl | 153 | 05 | (M+1) - water | 165 | 11 |
| | chlorine | 143 | 42 | (M+1) - alkenyl chlorine - hydrogen | 117 | 100 |
| | chlorine | 145 | 13 | (M+1) - alkenyl chlorine ± hydrogen | 119 | 79 |
| | | | (M+1) M alkenyl chlorine + hydrogen | 121 | 15 | |

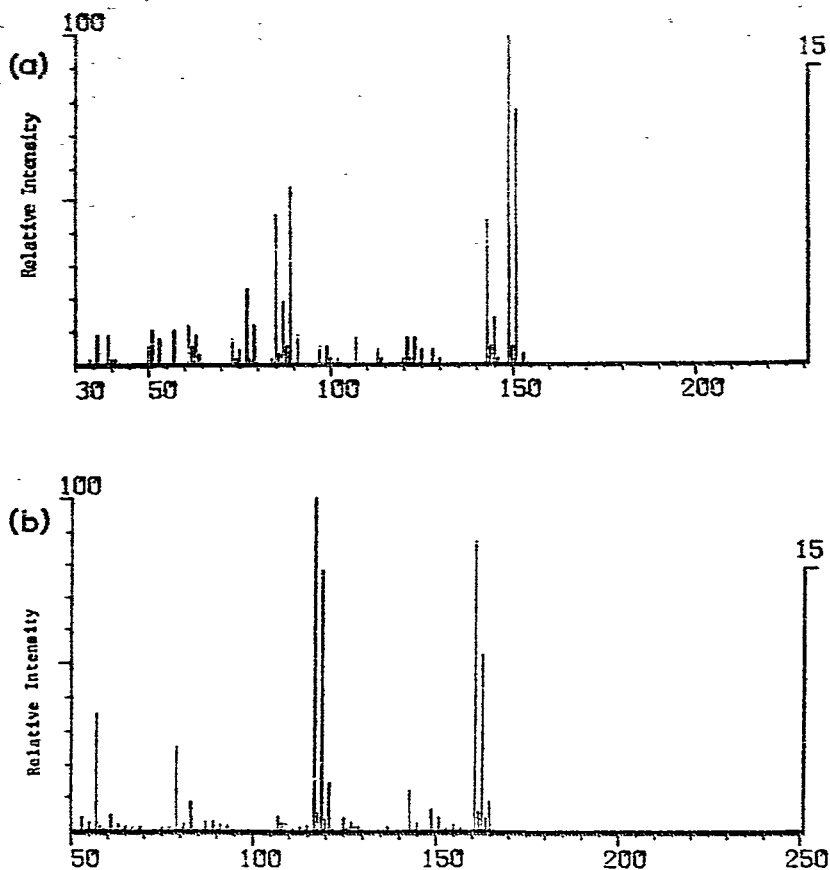


Fig. 5. Mass spectra of VI by (a) EI and (b) CI.

which was the secondary route for the other alcohols. Since the GC trace showed two peaks whose mass spectra were very similar, it is believed that these represent the two geometric isomers of compound IV. The order of elution from the gas chromatograph of the sample (Abbott) was V, III, I, and isomers of IV and VI. The CI spectra of III and IV exhibited loss of alkenyl chloride radical as the primary route. Although none of the alcohols possessed a $M + 1$ ion, the loss of water from the $M + 1$ ion was the secondary route with the exception of I, which exhibited dehydration as its major route. The dichloro derivative VI of ethchlorvynol exhibited large peaks at 161, 163 and 165 which were due to the loss of water from the protonated molecular ion; however the base peak was at m/e 117. Quite possibly the 117, 119 and 121 peaks were due to two different ions, each containing a single chlorine atom (^{35}Cl) with masses of 117 and 119. This is conceivable by the rearrangement of a chlorine atom to the $\text{C}_2\text{H}_5\text{-C}(\text{OH})(\text{C}\equiv\text{CH})\text{-}$ moiety accompanied by the gain (m/e 119) or loss (m/e 117) of a hydrogen atom. Other routes include loss of chlorine and loss of water and chlorine from the parent ion. 3-Pentanone was detected and compared to the EI spectrum of a known

sample. A parent peak, m/e 86 was present but the major peak was represented by loss of ethyl radical (m/e 57). The secondary route was loss of ethane (m/e 56) followed by loss of methyl (m/e 41).

The GC results showed that the amount of ethchlorvynol in capsules varied from 94.040% to 99.784%; the sample from the bottle consisted of 99.48% ethchlorvynol.

Although the concentration of the impurities was small compared with that of ethchlorvynol, it is essential from the toxicological point of view that these impurities be identified. This report showed that a number of tertiary alcohols similar in structure to ethchlorvynol are the major impurities. Work is in progress in our laboratory to study the acute and chronic toxicity of these compounds.

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