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# Degradation of (—)-ephedrine in solution and during extraction with diethyl ether

A. H. BECKETT*, G. R. JONES AND D. A. HOLLINGSBEE

*Department of Pharmacy, Chelsea College, University of London, Manresa Road, London, SW3 6LX, U.K.*

Significant losses occurred during the extraction of small quantities of ephedrine from aqueous media using either regular or analytical grades of diethyl ether. The losses were, at least in part, caused by reaction of the ephedrine with aldehydic impurities in the ether; three substituted oxazolidines were identified, using g.l.c. and g.l.c.-ms. These and one other oxazolidine were synthesized and characterized by g.l.c., g.l.c.-ms, nmr and infrared spectroscopy. Alternative mechanisms for ephedrine breakdown were considered. Ephedrine was separately oxidized by three different oxidizing agents and also irradiated by ultraviolet light; the products were characterized by g.l.c., g.l.c.-ms. A method for the purification of diethyl ether is recommended to minimize ephedrine breakdown.

Inconsistent calibration curves were obtained when diethyl ether was used for the extraction of small quantities of ephedrine from biological fluids, for assay by g.l.c. A reduction in the ephedrine/internal standard peak height ratios corresponded to an increase in size of at least two and sometimes three unidentified g.l.c. peaks. The possibility that these products might arise from the oxidation of ephedrine, or its degradation due to impurities in the ether, was investigated.

## MATERIALS AND METHODS

### *Compounds and reagents*

The following compounds were purchased: (−)-ephedrine anhydrous (Sigma), (−)-ephedrine hydrochloride, nickel peroxide, formaldehyde solution (40% w/w), acetaldehyde, propionaldehyde (all BDH), activated alumina (Woelm), diethyl ether SLR grade (BDH, M & B, and Fisons) and Analar grade (Fisons).

### *General method of analysis*

An aliquot of aqueous ephedrine solution (5 ml) was made alkaline with sodium hydroxide (5 M, 0·5 ml), n-butylamphetamine hydrochloride marker solution added (1 ml) for quantitative work and the solution extracted with freshly distilled Analar diethyl ether (2 × 10 ml). The combined ethereal extracts were evaporated to 50 $\mu$l in a water bath (45°) and examined by g.l.c.

### *Investigation of factors affecting the assay*

Sodium bicarbonate, potassium carbonate or ammonia solution was substituted for sodium hydroxide in the assay, to vary the pH of the solution between pH 9 and 14. The effect of substituting n-pentane as the extracting solvent and of adding n-butanol (25–50 $\mu$l per tube) to the ethereal extracts before their evaporation, was investigated. Purification of the diethyl ether was attempted by washing with water, sodium metabisulphite solution (10% aqueous), hydrochloric acid (M) and sodium hydroxide (5 M) before distillation. The effect of using different grades (Analar or SLR), different batches or different distillate fractions of diethyl ether was also investigated.

*Gas liquid chromatography* was carried out on a Perkin Elmer F11 instrument with a flame ionization detector, using a glass column, 1m, 0·40 cm i.d., packed with 2·0% Carbowax 20M and 5% potassium hydroxide on acid washed, DMCS treated Chromosorb G (100-120 mesh); oven temperature 100° (system 1; for identification of breakdown products) or 125° (system 2; for quantitative work); nitrogen carrier gas flow, 106 ml min$^{-1}$ (pressure 105 kPa). G.l.c. retention times are at oven temp. 100° unless otherwise stated.

*G.l.c. linked mass spectrometry (g.l.c.-ms)* was performed on a Perkin Elmer model 270 instrument using a glass column, 1 m, 0·40 cm i.d., packed as above. Helium 100 ml min$^{-1}$ was the carrier gas (100 kPa); the oven temperature 120–140° and the ionizing potential 70 eV.

*Direct inlet mass spectra* were recorded on an AE1 MS-9 or MS-12 instrument using an ionizing potential of 70eV.

* Correspondence.

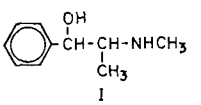
*Nuclear magnetic resonance spectra* were recorded on a Perkin Elmer R32 spectrometer incorporating a field lock on the TMS (tetramethylsilane) internal standard signal, as 10% solutions in $CDCl_3$.

*Infrared spectra* were recorded on a Perkin Elmer model 157G spectrophotometer as neat films or Nujol mulls between rock salt plates.

## RESULTS AND DISCUSSION OF THE ASSAY

### *General method of analysis—factors affecting ephedrine degradation*

Using the method described above, erratic results were obtained on repeated g.l.c. analysis of aqueous ephedrine solutions. The degree of 'breakdown' varied from day to day; it was often up to 0·005 $\mu$mol per assay, occasionally greater than 0·05 $\mu$mol per assay, though sometimes not detectable.

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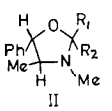


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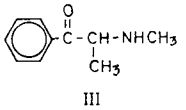



III

| Compound | $R_1$ | $R_2$ | G.l.c. Rt(min) system |
|---|---|---|---|
| I | — | — | 26·0 |
| IIa | H | H | 9·0 |
| IIbi | H | $CH_3$ | 7·6 |
| IIbii | $CH_3$ | H | 9·9 |
| IIci | H | $C_2H_5$ | 10·0 |
| IIcii | $C_2H_5$ | H | 12·6 |
| IId | $CH_3$ | $CH_3$ | 9·7 |
| III | — | — | 12·7 (dec.) |
| Ether impurity | | | 11·2 |

FIG. 1. Structures and g.l.c. retention times of some oxidation and possible oxidation products of ephedrine (I).

On g.l.c., two ephedrine 'breakdown' peaks were always observed and were identified by g.l.c.-ms. In most samples the peak of shorter retention time (IIbi, Rt 7·6 min) was larger than that of longer retention time (IIci, Rt 10·0 min); but the ratio of these peak heights was not constant. A third minor peak (IIa, Rt *ca* 9·1 min) was sometimes evident but g.l.c.-ms was not possible due to the small amount usually present. A further g.l.c. peak (Rt 11·2 min) was sometimes observed and was due to an impurity in some batches of ether (distilled or undistilled); the presence of this peak made it difficult to obtain even qualitative correlation of the effects of different factors (e.g. light, alkali, heat, air) with the degree of ephedrine decomposition.

Ephedrine breakdown was shown not to occur on the g.l.c. instrument as follows. Two ethereal ephedrine solutions of the same, low concentration were injected into the g.l.c. (system 2); the first was obtained by dissolving ephedrine base in ether and the other by dissolving the same amount of ephedrine in a much larger quantity of ether and evaporating to a similar concentration. The first solution gave only one peak on g.l.c. (due to ephedrine) whereas the second solution gave in addition, 'breakdown' peaks as described above. Changing the pH of the ephedrine solution extracted had no effect on the degree of breakdown. The addition of n-butanol to the ethereal extract before evaporation reduced the 'breakdown' that occurred if the extracts were allowed to boil dry in the water bath; for this reason its routine use is of value (provided aldehyde free n-butanol is used).

Of the experimental factors considered, the extracting solvent was found to cause the greatest degree of ephedrine breakdown. SLR grade ether produced consistently greater breakdown than the Analar grade and gave a larger number of 'ether impurity' peaks on g.l.c. Different batches of the same grade of ether also caused differences in the amount of breakdown occurring. Single complete distillation of the ether used did not significantly reduce the amount of ephedrine 'breakdown'; however middle fractions caused significantly less 'breakdown' than the first or last fractions. Undistilled Analar ether caused consistently less 'breakdown' of ephedrine than undistilled SLR grade ether and calibration curves obtained using the same batch of ether were reasonably consistent from day to day.

Consistent, low levels of ephedrine 'breakdown' (less than 0·0015 $\mu$ mol per assay) were achieved by prior washing of the ether (500 ml undistilled Analar grade) with sodium metabisulphite solution (10%, 50 ml) followed by hydrochloric acid (1M, 50 ml) and finally with sodium hydroxide (5M, 50 ml), the latter being the most effective if only a single wash was employed. This treatment also adequately eliminated the 'breakdown' caused by the deliberate contamination of ether with formaldehyde, acetaldehyde, and propionaldehyde. However, after subsequent storage, (greater than 24 h) the treated ether caused more ephedrine breakdown than it did before storage, possibly due to peroxide formed following removal of the stabilizer.

*Attempted acceleration of ephedrine breakdown*

Decomposition of (−)-ephedrine was less than 1% after the prolonged passage of air through cold (20°) or refluxing, neutral or basic aqueous solutions (0·2% w/v ephedrine hydrochloride in phosphate buffer pH 7·4 or in 1% sodium hydroxide). The observed products (g.l.c. analysis) probably arose through condensation of ephedrine with aldehydes in the ether used in the extraction. Similar solutions irradiated with ultraviolet light for 18 h showed slight discolouration, but the observed breakdown products (Ibi, IIci and/or IIbii) represented less than 1%. Negligible decomposition was observed on refluxing ephedrine base (0·5% w/v) in ether saturated with aqueous 20% sodium hydroxide, for 8 h, or ephedrine base (8% w/v) in ethanolic sodium hydroxide for 3 h.

Ephedrine base stored in ether (100 mg ml$^{-1}$) at room temperature (15–25°) in the light for several weeks decomposed to give IIa and IIbi. This is in contrast to the small amount of decomposition that occurred upon ultraviolet irradiation of *aqueous* solutions of ephedrine (0·2% w/v hydrochloride salt in phosphate buffer, pH 7·4 or in 1% sodium hydroxide). Solutions of ephedrine base (3% w/v) in ether or benzene were extensively degraded by ultraviolet light over 18 h (30 w power, λ254 nm, 20 cm from the sample). The main ether soluble products observed on g.l.c. systems 1 and 2 were IIbi and IIa (g.l.c.-ms evidence), in addition, ether insoluble resinous material was formed and ether soluble material with long g.l.c. retention times (not identified).

*Conclusion for analysis of ephedrine*

The major decomposition products yielding peaks upon g.l.c. examination after extraction of ephedrine solutions with ether and concentration of these extracts, arise from addition and condensation with ephedrine of acetaldehyde, propionaldehyde and/or formaldehyde impurities in the solvent. Minor products result from oxidation of ephedrine by small amounts of other impurities (e.g. peroxides) in the ether. Single distillation failed to remove these.

The solvent is best purified by washing with sodium metabisulphite solution, dilute hydrochloric acid, and by sodium hydroxide solution. The solvent should then be distilled and used within 24 h; any remaining should be discarded. The addition of 25–50 μl of aldehyde free n-butanol to each tube before evaporation of the ether is recommended.

These precautions may also be necessary to prevent losses during the extraction of *pseudo*-ephedrine and other related β-hydroxyamines which can react with aldehydes to form oxazolidines, or where the phenyl ring is activated such as in phenylephrine and the catecholamines, to form isoquinoline type structures.

CHEMISTRY

*Erythro-3,4-dimethyl-5-phenyloxazolidine (IIa)*

Formaldehyde solution (40% HCHO, 9 ml 120 mmol) in ethanol (96%, 50 ml) was added to a solution of (−)-ephedrine base (17·0 g, 103 mmol) in ethanol (96%, 100 ml) and left for 1½ h at room temperature. The solvent and water were removed and the product distilled *in vacuo* to yield the title compound as a colourless oil (16·6 g, 88%) b.p. 61–65°; 0·04–0·05 mmHg (cf. Pfanz & Kirchner, 1958; (±)-isomer, 80°, 0·5 mmHg); nmr δ 0·66 (d, $J$ = 6·6, 3 CHC$H_3$) 2·38 (s, 3, NC$H_3$), 2·88 (m, 1, C$H$CH$_3$) 4·07 (d, $J$ = 3·1, 1, C$H$H (4·87 (d, $J$ = 3·1, 1, CH$H$) 5·10 (d, $J$ = 7·2, 1, ArC$H$) 7·29 (s, 5, *Ar*); infrared (film) $\nu_{max}$ 700 (s), 715 (m), 755 (s), 1000 (s), 1065 (s), 1095 (m), 1145 (m), 1175 (m), 1210 (m), 1230 (s), 1320 (m), 1365 (m), 1380 (s), 1455 (s), 1495 (m), 2705 (m), 2795 (s), 2860–3000 (s) cm$^{-1}$; ms (direct inlet) *m/e* (% rel. abund); 177 (1·5, M$^{+\cdot}$) 176 (2), 175 (1·5), 106 (7), 105 (8), 77 (10), 72 (13), 71 (100), 56 (22), metastables (m*) at 44·2 and 26·0. Found: C, 74·9; H, 8·5; N, 8·0. Calc. for $C_{11}H_{15}NO$: C, 74·6; H, 8·5; N, 7·9%.

*Erythro-2,3,4-trimethyl-5-phenyloxazolidine (IIb)*

This was prepared in a similar manner to IIa using acetaldehyde (6·1 g, 139 mmol) and (−)-ephedrine base (20·0 g, 121 mmol) to give a colourless oil which was a disproportionate mixture of two diastereoisomers (19·6 g, 85% yield), b.p. 58–62°, 0·08 mmHg (cf. Pfanz & Kirchner, 1958; 87°, 1·0 mmHg); nmr (IIbi) δ 0·65 (d, $J$ = 6·0, 3, OCH′C$H'_3$) 1·45 (d, $J$ = 4·4, 3, CHCHC$H_3$) 2·20 (s, 3, NC$H_3$) 2·72 (m, 1, CHC$H$CH$_3$) 3·92 (q, $J$ = 4·4 OC$H'$CH$'_3$) 4·96 (d, $J$ = 7·8, 1, C$H$CHCH$_3$) 7·28 (s, 5, *Ar*) and a set of signals of 5–10% the intensity of those of IIbi identified as from the diastereoisomer IIbii; infrared (film) $\nu_{max}$ 700 (s), 720 (m), 755 (s), 780 (m), 1015 (s), 1070 (s), 1100 (m), 1140 (s), 1195 (s), 1230 (s), 1335 (s), 1345 (s), 1395 (m), 1450 (s), 1490 (m), 2785 (s), 2800 (s), 2980 (s) cm$^{-1}$; ms (direct inlet) *m/e* (% rel. abund.): 191 (3,M$^{+\cdot}$) 190 (5), 189 (4), 176 (4), 148 (14), 85 (100), 77 (11), 71 (10), 70 (3), 58 (19), 57 (23), 56 (12), metastables (m*) at 124·5, 57·7 and 38·2. Found: C, 75·4; H, 8·8; N, 7·3; Calc. for $C_{12}H_{17}NO$: C, 75·4; H, 8·9; N, 7·3%.

*Erythro-2-ethyl-3,4-dimethyl-5-phenyloxazolidine (IIc)*

This was prepared in a similar manner to IIa from propionaldehyde (4·9 g, 85 mmol) and (−)-ephedrine base (10·0 g, 61 mmol) to give a colourless oil (10·6 g,

85% yield). (cf. Pfanz & Kirchner, 1958; 109°, 2·2 mmHg) b.p. 80°, 0·4 mmHg; nmr δ 0·65 (d, $J$ = 6·2, 3, $CHCH_3$) 1·08 (t, $J$ = 6·8, 3, $CH_2CH_3$) 1·75 (m, 2, $CH_2CH_3$) 2·23 (s, 3, $NCH_3$) 2·75 (m, 1, $CHCH_3$) 3·78 (dd, $J$ = 6·0, 1, $CHCH_2$) 4·98 (d, $J$ = 7·4, 1, ArC*H*) 7·30 (s, 5, *Ar*)—IIci and in addition a set of signals of *ca* 5% intensity assumed to be due to a diastereoisomer, IIcii; infrared (film) $\nu_{max}$ 705 (s), 755 (s), 1025 (s), 1070 (s), 1140 (m), 1195 (s), 1220 (s), 1345 (s), 1455 (s), 1490 (m), 2800 (s), 2970 (s) $cm^{-1}$; ms (direct inlet) *m/e* (% rel. abund.): 205 (0·3, $M^{+\cdot}$), 204 (1), 176 (19), 148 (38), 116 (10), 105 (10), 99 (100), 91 (17), 84 (46), 77 (10), 56 (10), 42 (22), metastables (m*) at 124·5, 119·5 and 71·3. Found: C, 75·8: H, 9·2; N, 6·8. Calc. for $C_{13}H_{19}NO$: C, 76·1; H, 9·3; N, 6·80.

*Erythro-2,2,3,4-tetramethyl-5-phenyloxazolidine (IId)*
(−)-Ephedrine base (10·0 g, 61 mmol) was refluxed in acetone (150 ml, 2·0 mol) for several days, after which time only half the ephedrine had reacted. Activated alumina (20 g, grade 1) was added, and the solution refluxed for a further 2 h, after which the reaction was complete. The alumina was removed by filtration, the excess acetone removed and the product distilled *in vacuo*. The first fraction (1·4 g, b.p. 30°/0·25 mmHg) was concluded to be diacetone alcohol (nmr and infrared evidence). The second fraction (81°/0·3 mmHg) was the title compound, solidifying as oily crystals (9·5 g, 76% yield) which were recrystallized from ether–n-pentane over an acetone–solid $CO_2$ bath, m.p. 42–44° (cf. Hyne, 1959; 39–43°); nmr δ 0·60 (d, $J$ = 6·0, 3, $CHCH_3$) 1·19 (s, 3, $CCH_3$) 1·49 (s, 3, $CCH'_3$) 2·22 (s, 3, $NCH_3$) 3·12 (m, 1, $CHCH_3$) 5·02 (d, $J$ = 7·1, 1, ArC*H*); infrared (Nujol) $\nu_{max}$ 700 (s), 755 (m), 1030 (s), 1040 (s), 1050 (s), 1170 (m), 1205 (s), 1225 (m), 1265 (s), 1320 (m), 1360 (s), 1375 (s), 1450 (s), 1490 (m), 2790 (w), 2840–3000 $cm^{-1}$; ms (direct inlet), *m/e* (% rel. abund.): 205 (0·4, $M^{+\cdot}$), 190 (30), 148 (100), 132 (11), 117 (13), 105 (11), 99 (71), 91 (23), 84 (30), 77 (20), 71 (25), 58 (18), 56 (57), 51 (14), 43 (27), 43 (33), metastables (m*) at, 119·5, 115·3, 103·7 and 92·5. Found: C, 76·3; H, 9·4, N, 6·8. Calc. for $C_{13}H_{19}NO$: C, 76·1; H, 9·3; N, 6·8%.

*2-Methylamino-1-phenyl-1-propanone (III)*
(−)-Ephedrine (1·0 g, 6·1 mmol) was refluxed in benzene (50 ml) with 'active silver carbonate' on Celite (10·1 g ≡ to 18 m mol $Ag_2CO_3$) (Fetizon & Golfier, 1968) in a Dean and Stark apparatus until no more water was collected (60 min). The Celite/silver carbonate residues were filtered and washed, and the combined organic layers extracted with 2 M hydrochloric acid (2 × 20 ml). The acid layers were basified and extracted with ether (3 × 20 ml), the ether extracts dried (anhyd. $MgSO_4$) and the basic components precipitated with HCl gas (0·46 g yield). The salt was recrystallized from ethanol–ether to give the title compound as an off-white solid (0·33 g, 33% yield), m.p. 170–178° (with decomp.), (cf. Takamatsu, 1956, 173–175°) nmr (extracted from HCl salt in $D_2O$) δ 1·30 (d, $J$ = 6·4, 3, $CHCH_3$) 2·38 (s, 3, $NCH_3$) 4·22 (q, $J$ = 6·4, 1, C*H*) 7·3–8·1 (2 m, 3 + 2, *Ar*); infrared (HCl salt in Nujol) $\nu_{max}$ 700 (s), 900 (m), 975 (m), 1005 (m), 1245 (m), 1300 (m), 1360 (m), 1380 (m), 1460 (s), 1575 (m), 1590 (m), 1685 (s, C = O), 2450 (m), 2700 (s, $NH_2^+$), 2840–3000 (s) $cm^{-1}$; ms (direct inlet, HCl salt), *m/e* (% rel. abund.): 164 (0·6, M + 1), 163 (0·3, $M^{+\cdot}$), 105 (3), 77 (11), 58 (100), 56 (10), 51 (4), 42 (4), 36 (6), metastables (m*) at 56·5. Found: C, 59·6, H, 7·1; N, 6·9; Cl, 18·0. Calc. for $C_{10}H_{14}NOCl$: C, 60·2; H, 7·0; N, 7·0; Cl, 17·8%.

*Oxidation of (−)-ephedrine base with nickel peroxide*
(−)-Ephedrine base (0·03 g) was shaken for 15 min with nickel peroxide (0·01 g), in ether. The products were qualitatively examined by g.l.c. The product of oxidation of ephedrine base with nickel peroxide, gave peaks due to benzaldehyde (Rt 1·4 min) and the oxazolidines IIbi (Rt 7·6 min) and IIbii (a diastereoisomer of IIbi, Rt 9·9 min, 10% peak height of IIbi) on g.l.c. system 1.

*Oxidation of (−)-ephedrine base with 'active silver carbonate'*
The product of oxidation of ephedrine with 'active silver carbonate' gave two peaks on g.l.c. (system 1 or 2); a sharp peak at 12·7 min, merging into a much broader peak centred at *ca* 15 min, which tailed extensively away from the solvent front towards the ephedrine peak. A small amount of benzaldehyde and a negligible quantity of IIbi were also formed. A g.l.c.-ms run of the 12·7 min peak showed the base ion at *m/e* 58 with an *m/e* 56 ion increasing rapidly in intensity as subsequent scans were made, the *m/e* 58 ion rapidly decreasing in intensity. The main product isolated from the reaction was 2-methylamino-1-phenyl-1-propanone (III). See also the g.l.c. properties of III below, and under the syntheses.

*Oxidation of (−)-ephedrine base with 'active manganese dioxide'*
(−)-Ephedrine base (10·0 g, 61 mmol) was stirred in ether (100 ml) with 'active manganese dioxide' (65 g; prepared as described by Attenburrow, Cameron & others, 1952) at room temperature for 1 h. The manganese dioxide was removed by filtration, washed with ether and the residue discarded. The combined ethereal filtrates were examined qualitatively by g.l.c. and g.l.c.-ms.

A mixture of products similar to those from both the above oxidations was obtained.

## DISCUSSION OF THE CHEMISTRY

*Synthesis of the oxazolidines*
Products of the condensation of ephedrine with aldehydes exist almost entirely in the oxazolidine

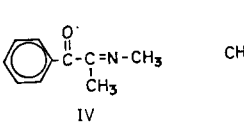
form, unlike the corresponding norephedrine analogues which exist substantially as the Schiff base (Bergmann, 1953; Pfanz & Kirchner, 1958). None of the oxazolidine compounds synthesized showed an infrared absorption in the region 1650–1690 $cm^{-1}$ that could be attributed to the imine C=N stretching frequency, nor did the spectra show significant OH absorption bands in the region 3200–3400 $cm^{-1}$. Also, the mass spectra are most consistent with an oxazolidine type structure (II) rather than an imine type structure.

Precipitation of the HCl salt of IIa from dry ether, with HCl gas, was successful; however it partially decomposed to ephedrine on an attempted recrystallization; similar results were obtained for IIb. All the oxazolidines (IIa–IId) partially decomposed on t.l.c. to ephedrine (g.l.c. evidence) using silica gel G, or neutral alumina plates run in a variety of organic solvents.

G.l.c.-ms provided almost the sole means of identifying some of the breakdown products of ephedrine due to their similar g.l.c. properties and lability on t.l.c. In low concentrations it was not possible to distinguish between IIci, IId and IIbii on g.l.c.; g.l.c.-ms however, indicated the identity and composition of such peaks after concentration of the extracts. A g.l.c.-ms of one of the ephedrine breakdown products indicated it could be due to a compound having structure IIc or IId; both these oxazolidines were therefore synthesized and found to have similar g.l.c. retention times. However, IIc and IId were readily distinguished by g.l.c.-ms; IIc gives a substantial *m/e* 176 (19%) ($M^{+\cdot}$-Et) whereas IId does not, but instead gives a moderately strong *m/e* 190 (32%) ion ($M^{+\cdot}$-Me), which is absent in IIc. Each of the compounds IIa–IId were characterized by the loss of a mass 106 (probably benzaldehyde from the molecular ion) with consequent retention of the charge on the remaining fragment [*m/e* 71 (100%) from IIa, *m/e* 85 (100%) from IIb, *m/e* 99 (100%) from IIc and *m/e* 99 (65%) from IId], and the presence of ions due to the loss of a methyl radical from the ($M^{+\cdot}$-PhCHO) ions: [*m/e* 56 (22%) from IIa, *m/e* 70 (30%) from IIb, *m/e* 84 (46%) from IIc and *m/e* 84 (8%) from IId]. In addition, *m/e* 148 ions were present in the spectra of IIb–IId (14, 38 and 100% rel. abund. respectively and are accounted for by the loss of $C_2H_4$ from an *m/e* 176 ion (m* 124·5) with IIb and IIc and $C_3H_6$ or $C_2H_4N$ from an *m/e* 190 ion (m* 115·3) with IId.

*G.l.c. properties and g.l.c.-ms of 2-methylamino-1-phenyl-1-propanone* (III)

Compound III was isolated from the product of oxidation of ephedrine with 'active silver carbonate'; it gave a peak on g.l.c. at 12·7 min (salt or base) which tailed sharply away from the solvent front indicating breakdown, and had the same g.l.c.-ms characteristics as the 12·7 min peak of the oxidation mixture from which it was obtained. In the g.l.c.-ms of the tail of the g.l.c. peak the base ion (*m/e* 56) is at least ten times the intensity of the next most intense ion (*m/e* 58), and may be due to ion $CH_3\text{-}C{\equiv}\overset{+}{N}\text{-}CH_3$ or $CH_2{\equiv}C{=}\overset{+}{N}H\text{-}CH_3$ either of which could readily arise from structure 4 in a manner similar to the formation of $CH_3\text{-}CH{=}\overset{+}{N}HCH_3$ (*m/e* 58) from 3 (direct inlet ms) or ephedrine.

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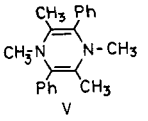
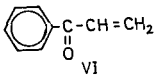



V




VI

Simple g.l.c. breakdown of III to IV by loss of hydrogen is unlikely unless disproportionation into IV and ephedrine (I) occurs. Structure V (above) is an alternative which could arise through the addition of two molecules of III and subsequent loss of two molecules of water. However, mass spectral fragmentation of V to form such an intense *m/e* 56 base ion is unlikely; also, ions greater than *m/e* 165 were not observed. G.l.c. breakdown of the α-amino-ketone, 3 to 1-phenylprop-2-en-1-one (VI) and methylamine, whilst possible, is not consistent with the g.l.c.-ms evidence obtained of the main g.l.c. peak. The HCl salt of III, gives the same g.l.c.-ms breakdown pattern as the base (α-amino-ketones are much more stable as a strong salt, than in basic media; Takamatsu, 1956).

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