Tetrahedron. Vol. 31, pp. 1531 to 1535. Pergamon Press 1975.

SYNTHETIC ROUTES TO OPTICAL ISOMERS OF PRIMARY AND SECONDARY HYDROXYLAMINES OF 1-ARYLISOPROPYLAMINES

A. H. BECKETT,* K. HAYA, G. R. JONES and P. H. MORGAN
Chelsea College, University of London, Manresa Road, London SW3 6LX

(*Received in UK* 4 *December* 1974; *Accepted for publication* 12 *February* 1975)

Abstract—A number of optically pure primary 1-arylisopropylamines were converted to 3-phenyl-2-(1′-arylisopropyl)oxaziridines by the oxidation of the corresponding benzylimines with *m*-chloroperbenzoic acid. Subsequent acid hydrolysis of the 3-phenyloxaziridines yielded optically pure N-hydroxy-1-arylisopropylamines. The action of *m*-chloroperbenzoic acid on optically pure secondary 1-arylisopropylamines gave optically pure N-hydroxy derivatives. The optical purity of the hydroxylamines were analysed by GLC utilizing N-trifluoroacetyl-L-prolyl chloride as a reagent.

INTRODUCTION

An important metabolic route for many primary and secondary aliphatic amines is N-oxidation to yield labile hydroxylamines, which further metabolize or are chemically converted to amines, ketones or aldehydes.[1–7] Synthetic samples of N-hydroxy derivatives of amines were therefore required to help identify the metabolites and some were required in their optically active forms.

An obvious route to optically pure secondary hydroxylamines would be the previously reported method[8] of preparing hydroxylamines from secondary amines since the asymmetric centre is not involved; the route was examined using a representative number of optically pure secondary 1-arylisopropylamines. On the other hand, preparation of primary hydroxylamines has previously required catalytic reduction of the corresponding oxime[9] or the nitro-olefin[10] or the reduction of a nitro-olefin with lithium aluminium hydride.[11] These methods cannot be used directly to prepare the optical isomers of N-hydroxyamphetamine (**4**) and related primary hydroxylamines, since the optically active centre at the α-carbon is not present in the precursor intermediate. A direct method was therefore sought for the synthesis of optically active hydroxylamines from optically active primary amines with retention of optical purity.

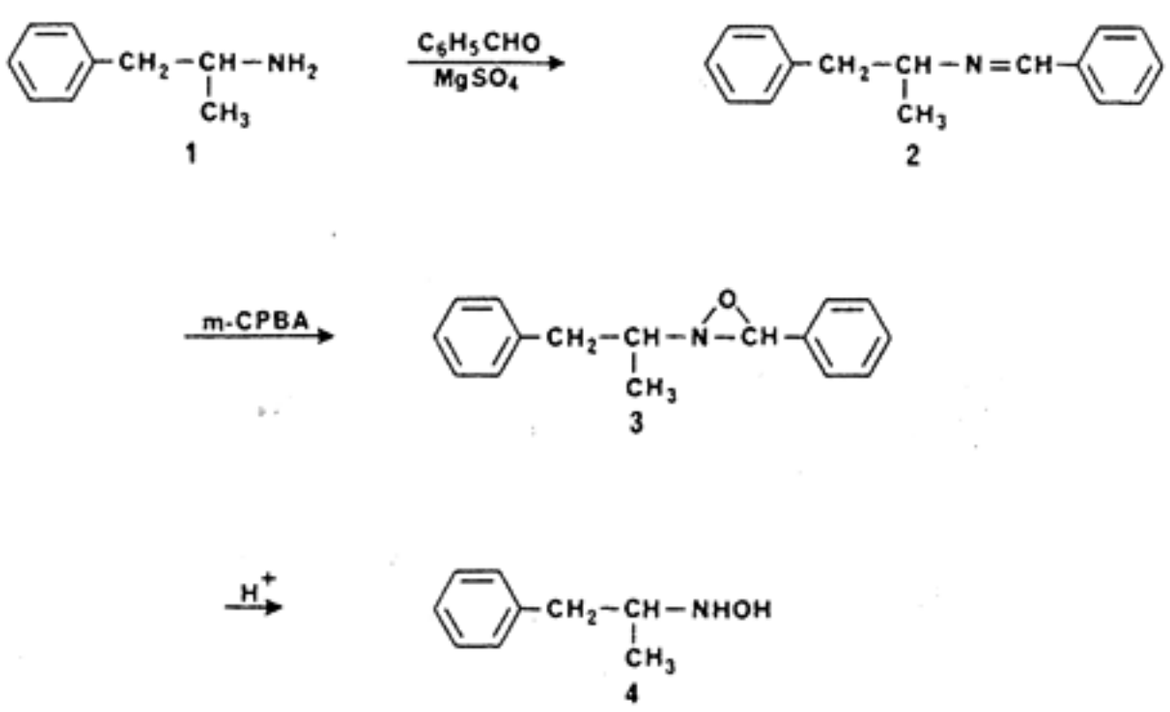


Fig. 1. Synthetic route to N-hydroxyamphetamine (**4**).

RESULTS AND DISCUSSION

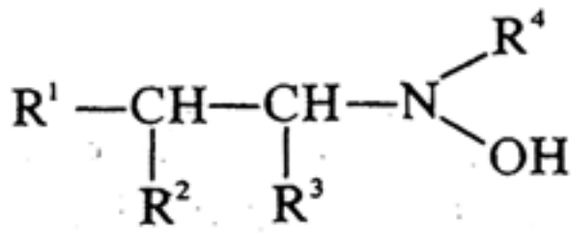
Primary hydroxylamines. It is known that 3-phenyloxaziridines, e.g. **3**, are converted in acid solution to the corresponding hydroxylamine, e.g. **4**, with the loss of aromatic aldehyde.[12] It seemed probable that if suitable means could be found for converting optically active primary amines having α-asymmetric centres to the oxaziridine with retention of optical purity, then the acid hydrolysis could be carried out without loss of optical purity. A further advantage would be that the method could be used for preparing primary hydroxylamines directly from the corresponding amines used as drugs or produced as metabolites of drugs.

The successful method developed is exemplified by the preparation of (+)-N-hydroxyamphetamine (**4**). The reaction of (+)-amphetamine (**1**) with an excess of benzaldehyde in CH_2Cl_2 containing dried $MgSO_4$ at room temperature gave the imine (**2**). GLC analysis (system A) of the reaction mixture indicated the formation of **2** to be complete after 2 hr, i.e. the peak due to **1** disappeared with the appearance of a new peak corresponding to the imine. The magnesium sulphate was removed by filtration and an excess of *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 was added to the filtrate. Oxidation of imines with *m*-CPBA has been shown to be a useful method for the preparation of 3-phenyloxaziridines.[13] The oxidation was continued for 2 hr at room temperature, at which time a GLC analysis (System A) of the mixture indicated the reaction was complete. The disappearance of the peaks due to **2** was accompanied by the appearance of two peaks, R_t = 9·6, 11·8 min. The peak at R_t = 9·6 min was probably due to the partial breakdown of 3 - phenyl - 2 - (1′ - phenylisopropyl)oxaziridine (**3**) to the isomeric nitrone during GLC analysis at the oven temperature (185°) used.[12] This was supported by the GLC analysis (System A) of an authentic sample of the nitrone.[8] The peak at R_t = 11·8 was then presumed to be due to **3**.

Hydrolysis of 3-phenyloxaziridines in methanolic sulphuric acid gives hydroxylamines[12] and other studies have demonstrated that the hydrolysis of 3-phenyloxaziridines becomes maximum at a 2M concentration of perchloric acid.[14] Thus, **3** was subjected to a 2-3M methanolic sulphuric acid solution for 18 hr at room temperature. (+)-N-Hydroxyamphetamine was subsequently isolated in 34% yield as the neutral oxalate salt. Other primary hydroxylamines that were prepared in a similar manner are listed in Table 1.

Secondary hydroxylamines. Optically pure secondary hydroxylamines were prepared by oxidizing the optically pure secondary amine with *m*-CPBA followed by LAH reduction.[8] The secondary hydroxylamines prepared are also listed in Table 1.

Table 1. Primary and secondary hydroxylamines prepared



Hydroxylamine of -	R^1	R^2	R^3	R^4	Melting Point (°C) Base	Melting Point (°C) Oxalate	% yield[a]	R_t of TPC derivative of amine (min)[b]	Peak Ht. Ratio[c] amine[d]	Peak Ht. Ratio[c] reduced hydroxylamine[e]
(±)-Amphetamine	C_6H_5	H	CH_3	H	60.5-62	167-169	41			
(+)-Amphetamine	C_6H_5	H	CH_3	H	78.5-81	167-169	34	13.3(S), 18(L)	0.15	0.17
(-)-Amphetamine	C_6H_5	H	CH_3	H	78.5-81	167-169	28	14.3(L), 17.8(S)	0.22	0.24
(±)-Norfenfluramine	3'-$CF_3C_6H_5$	H	CH_3	H	67-69	165.5-167	11			
(+)-Norfenfluramine	3'-$CF_3C_6H_5$	H	CH_3	H	82-85	177-180 (dec)	18	12.6(S), 17.2(L)	0.15	0.15
(-)-Norfenfluramine	3'-$CF_3C_6H_5$	H	CH_3	H	82-85	177-180 (dec)	18	13.4(L), 15.6(S)	0.12	0.13
(±)-Norephedrine	C_6H_5	OH	CH_3	H		170-172	39			
(+)-Norpseudoephedrine	C_6H_5	OH	CH_3	H	51-53	144-145	34			
Phenylethylamine	C_6H_5	H	H	H	84-85.5	170-175 (dec)	28			
(±)-2-Amino-1-(2',6'-Dimethylphenoxy) Propane	2',6'-$(CH_3)_2C_6H_5O$	H	CH_3	H	71.5-72.5	130.5-131.5	46			
(±)-3,4-Dimethoxy-amphetamine	3',4'-$(CH_3O)_2C_6H_5$	H	CH_3	H	75-77	137-139	7			
(±)-2-Amino-1-(3'-Trifluromethylthiophenyl) Propane	3'-$CF_3SC_6H_5$	H	CH_3	H		126-130	7			
(+)-Fenfluramine	3'-$CF_3C_6H_5$	H	CH_3	C_2H_5		151-153	29	17.6(S), 21(L)	0.11	0.13
(-)-Fenfluramine	3'-$CF_3C_6H_5$	H	CH_3	C_2H_5		151-153	30	17.4(L), 20.4(S)	0.10	0.08
(+)-Methylamphetamine	C_6H_5	H	CH_3	CH_3		140-142	36	22(S), 27(L)		0.15[f]
(+)-Ethylamphetamine	C_6H_5	H	CH_3	C_2H_5		138-140	21	22.4(S), 26.4(L)	0.11	0.11
(-)-Ethylamphetamine	C_6H_5	H	CH_3	C_2H_5		138-140	21	23.1(L), 31.2(S)	0.10	0.10
(+)-n-Propylamphetamine	C_6H_5	H	CH_3	C_3H_7		142-144	14	25.4(S), 30.3(L)	0.05	0.05
(-)-n-Propylamphetamine	C_6H_5	H	CH_3	C_3H_7		142-144	5	27.4(L), 30(S)	0.06	0.06

Footnotes:

a Based on moles of amine salt.

b GLC system B; (S) Small peak, (L) Large peak.

c Peak Ht. Ratio = Peak Ht.(S) ÷ Peak Ht. (L).

d of amine used in synthesis.

e of amine obtained from reduction of hydroxylamine.

f Compared with that of (+)-Amphetamine.

The yields of the hydroxylamines were based on the quantity of amine salt used for the reaction; the yields of most of the hydroxylamines are adequate since they could be prepared directly from the parent amine; no detailed attempts were made to optimize the reaction conditions.

Analysis of optical purity of the hydroxylamines

Primary hydroxylamines. The utility of the above method to prepare primary hydroxylamines is that optically active primary hydroxylamines can be made from the corresponding optically active 1-arylisopropylamines, many of which are important drugs or drug metabolites. A suitable method was then required to show the retention of optical purity in the method employed. Derivatisation with N - trifluoroacetyl - L - prolyl chloride ((−)-TPC) of optically active ephedrines to form diastereoisomers followed by GLC was used successfully to separate the optical isomers.[15] However, derivatisation with (−)-TPC of the optical isomers of the primary hydroxylamines proved to be inadequate. For example, (+) - N - hydroxyamphetamine (**4**) did not derivatise with (−)-TPC readily and GLC analysis (System B) indicated a mixture of the (−)-TPC derivatives of (+)-**4** as well as of (+)-amphetamine (**1**), the latter resulting from a breakdown of (+)-**4** to (+)-**1** which subsequently derivatised to give an interfering peak on GLC analysis, since (+)-**1** was shown to be absent in the primary hydroxylamine sample (see later).

Since primary hydroxylamines break down on the column during GLC analysis to the corresponding oxime and amine,[16] a derivative stable to GLC analysis was sought. The trimethylsilyl (TMS) derivative of N-hydroxyamphetamine was formed quantitatively and was stable. A sample of (+)-**4** from the same batch used for the derivatisation with (−)-TPC was derivatised with N-trimethylsilylimidazol (TSIM), which is known to silanise OH but not amino groups.[17] Only one peak due to the TMS derivative of (+)-**4** was obtained on GLC analysis (System A); this was confirmed by analysing samples of TSIM plus authentic (±)-**4**[11] and TSIM plus amphetamine (**1**). Thus, the above reaction of (−)-TPC with (+)-**4** must have converted some of the hydroxylamine (**4**) to the amine (**1**).

The method finally adopted to determine the optical

purity of the primary hydroxylamines was to first reduce them with LAH to the primary amine which was then derivatised with (−)-TPC and analysed by GLC (System B). The chromatograms obtained were then compared to those obtained from the (−)-TPC derivatives of the starting primary amines used for the synthesis of the hydroxylamines. An example of the type of chromatograms obtained are shown in Fig. 2. In all cases, using secondary

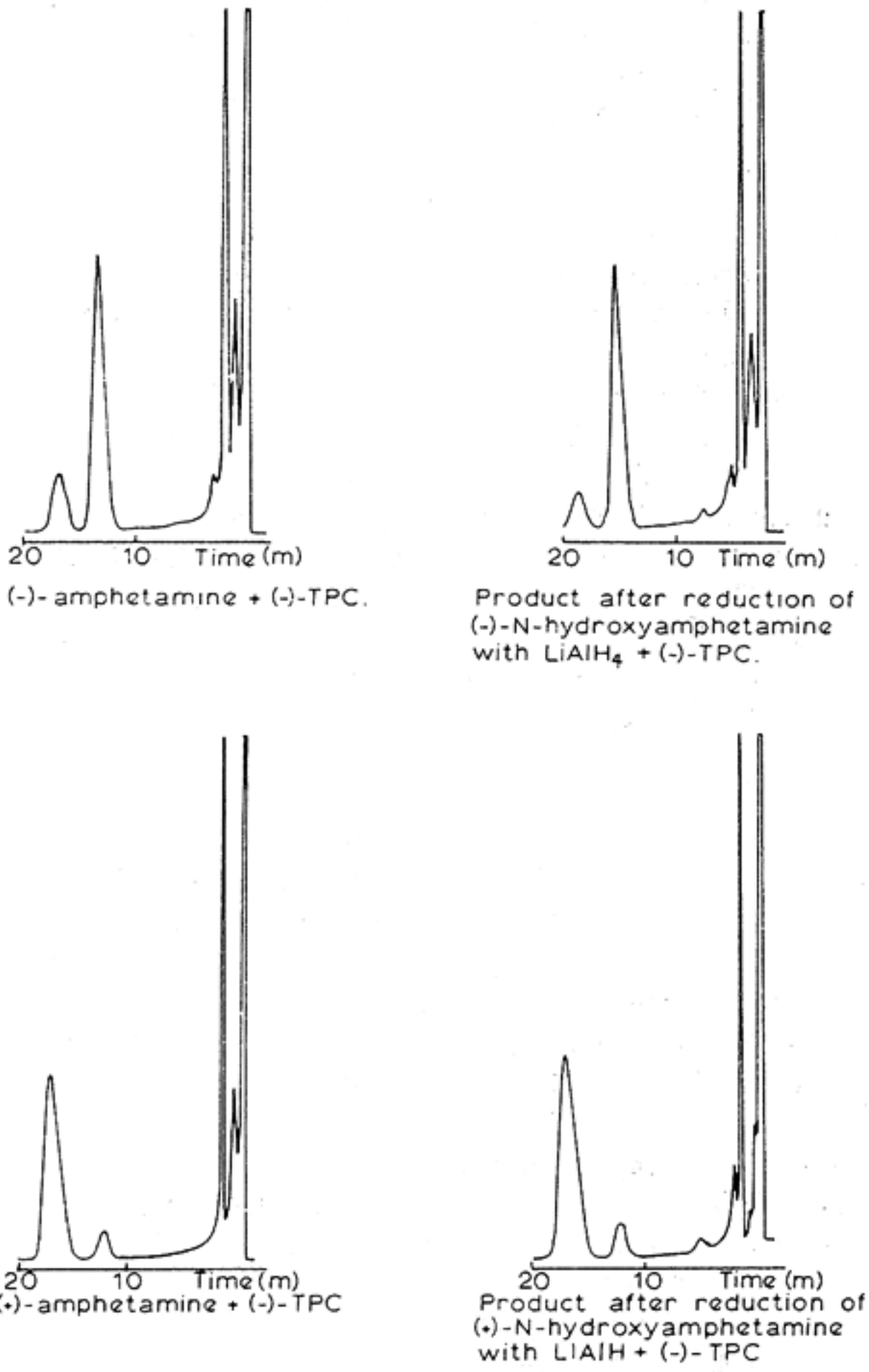


Fig. 2. Gas chromatograms for the analysis of optical purity of (+)- and (−)-N-hydroxyamphetamine.

and primary amines, the (−)-TPC derivative of th (−)-amine had a shorter retention time than that of the (+)-amine. In each case the chromatogram showed a large peak followed or preceeded by a smaller peak. The small peak is probably due to the optical impurity of (−)-TPC rather than optical impurity of the starting amine, since it is known that the (−)-TPC reagent used contains a certain amount of (+)-TPC.[18] The ratio of the peak height of the small peak to the peak height of the large peak of the starting amine was compared to that for the amine obtained from the reduction of the optically active primary hydroxylamine. For example, the peak height ratio of the (+)-amphetamine used for the synthesis of (+)-**4** was 0·15 and that of the (+)-**1** obtained from the reduction of (+)-**4** was 0·17. Thus, it can then be concluded that the optical purity of the two samples are essentially equal and that (+)-**4** was successfully synthesised from (+)-**1** with a complete retention of optical purity. A similar set or results were found for (−)-**4** and for (+)- and (−)-norfenfluoramine (Table 1).

Secondary hydroxylamines. The secondary hydroxylamines were unreactive to (−)-TPC and therefore they were reduced with acidic titanous chloride to the corresponding amine prior to derivatisation. With (+)- and (−)-N-hydroxy-N-ethyl and N-hydroxyl-N-propylamphetamine, the reduction produced the secondary amine and very little reductive dealkylation to (+)- and (−)-**1**. However, with (+)- and (−)-N-hydroxyfenfluramine, approximately equal amounts of (+)- and (−)-norfenfluramine and fenfluramine was obtained. However, the (−)-TPC derivatives of fenfluramine and norfenfluramine were sufficiently separated on the column used Fig. 3 and the optical purity of the products could therefore be determined.

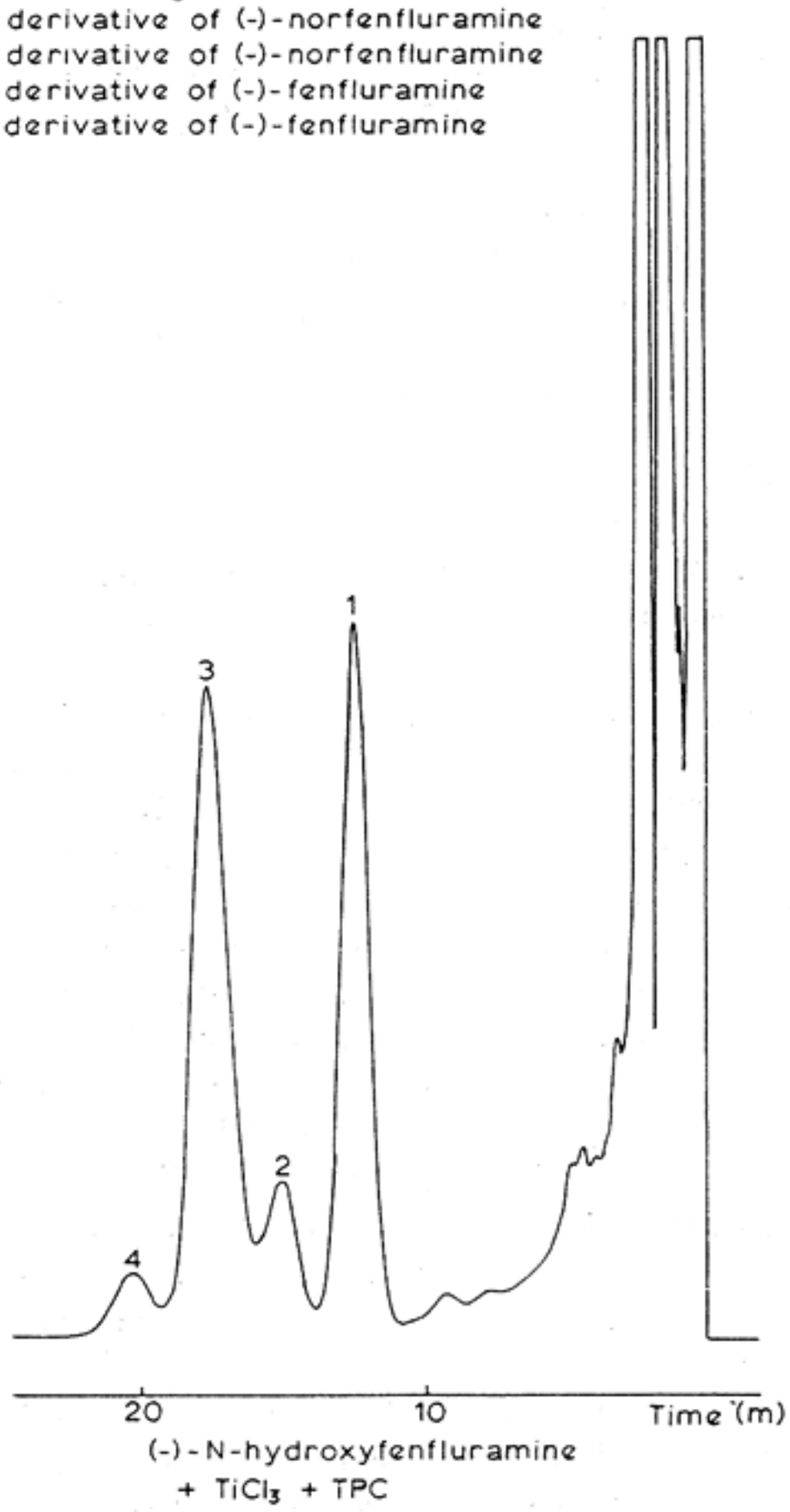


Fig. 3. Gas chromatogram for the analysis of purity of (−)-N-hydroxyfenfluramine.

Reduction of (+)-N-hydroxy-N-methylamphetamine gave predominantly (+)-**1**, i.e. N-demethylation occurred. The peaks resulting from the derivatisation of (+)-**1** formed from the reductive dealkylation were used to calculate the peak height ratios which were compared to that of the (−)-TPC derivative of an authentic sample of (+)-amphetamine. The results from the GLC analysis are given in Table 1.

By comparing the appropriate peak height ratios, it can be seen that the secondary hydroxylamines prepared e.. of the same optical purity as those of the starting amine. Thus the oxidation of optically active secondary amines with *m*-CPBA followe i by reduction with LAH is a successful method of preparing optically pure secondary hydroxylamines.

The above methods therefore, allow the direct synthesis of optically active primary and secondary hydroxylamines from the parent optically active secondary or primary amines of drugs and their metabolites.

EXPERIMENTAL

Methods. All m.ps are reported uncorrected. IR spectra were recorded on a Unicam SP 1000 spectrophotometer and NMR spectra were recorded on a Perkin Elmer R-32 spectrophotometer.

The solns for NMR were approx. 10% and TMS was used as the internal standard. Mass spectra of the oxalates were recorded on a Perkin Elmer Model 270 using the solid probe technique. GLC analyses were performed on a Perkin Elmer F-11 instrument equipped with a flame ionization detector. Systems used were: (A) glass column, length 2 m, o.d. 0·25 in containing 2% XE-60 on Chromosorb G HP, 80–100 mesh, N_2 as carrier gas, N_2 pressures and oven temps as specified later; (B) glass column, length 1 m, o.d. 0·25 in containing 2% OV-225 on Chromosorb W AW-DMCS, 80–100 mesh, oven temp 145°, carrier gas N_2 at 15 psi. Elemental analyses were performed by Dr. A. J. Layton, University College, London.

Compounds. All the data given are those obtained from the hydroxylamine bases unless indicated. The bases were liberated from their oxalates with $NaHCO_3$ solution or pH 7·4 phosphate buffer and extracted with ether.

(+)-Amphetamine sulphate, (−)-Amphetamine and (±)-3,4-dimethoxyamphetamine HCl were gifts from Smith Kline and French Laboratories, (±)-, (+)- and (−)-norfenfluramine and -fenfluramine were gifts from Servier Laboratories, 2 - amino - 1 - (3′ - trifluoromethylthiophenyl) propane, a gift from Synthelabo (France), 2 - amino - 1 - (2′,6′ - dimethylphenoxy) propane a gift from Boehringer (Ingleheim). The optical isomers of N-ethyl-and N-propyl-amphetamine were prepared from those of amphetamine.[19] The other amines used are available commercially. The secondary hydroxylamines were prepared according to a previously reported method.[8]

(+)-N-*Hydroxyamphetamine* (**4**). (+)-Amphetamine (**1**) was liberated from its sulphate (9·2 g, 0·05 mol) with 20% NaOH and extracted with CH_2Cl_2. The pooled CH_2Cl_2 extracts were dried and made up to 75 ml with CH_2Cl_2. Dried $MgSO_4$ (8·7 g, 0·05 mol) was added. A soln of benzaldehyde (10 g, 0·1 mol) in 25 ml of CH_2Cl_2 was added dropwise and the mixture stirred at room temp. for 2 hrs. The formation of the imine was shown to be complete at this time by GLC analysis (System A) of a sample of the mixture. The peak due to amphetamine disappeared and the imine peak reached a maximum height for a 2μl sample (R_t of amphetamine = 3·2 min, oven temp. = 90°, N_2 pressure = 15 psi; R_t of imine (2) = 1·2 min, oven temp. = 185°, N_2 pressure = 25 psi). After filtration, a soln of *m*-CPBA (12·1 g, 0·07 mol) in 150 ml of CH_2Cl_2 was added dropwise, and the mixture stirred at room temp. for 2 hr. GLC analysis (System A, oven temp. = 185°, N_2 pressure = 25 psi) showed two peaks at R_t = 9·6, 11·8 min with the absence of a peak at R_t = 1·2 min where the imine was expected. After filtration, the CH_2Cl_2 was removed under vacuum and 300 ml of 10% K_2CO_2 soln added to the residue. The basic soln was extracted with 3 × 200 ml of ether, the combined ether extracts were dried and concentrated under vacuum. The residue was dissolved in 50 ml of MeOH and added dropwise to a H_2SO_4:MeOH mixture (32 ml conc H_2SO_4, 75 ml MeOH, diluted to 200 ml with H_2O) at 0–5°. The resulting suspension was stirred at room temp. for 18 hr. The mixture was concentrated under vacuum in a cold water bath and then diluted with 200 ml of H_2O, and extracted with 3 × 150 ml of ether. The aqueous layer was partially neutralized with 200 ml of 20% NaOH at 0–5°. The neutralization was completed by the addition of solid $NaHCO_3$ and filtered. The filtrate was extracted with 3 × 250 ml of ether. The pooled ether extracts were dried over $MgSO_4$ and concentrated to approx. 100 ml and a saturated ethereal soln of oxalic acid was added. After cooling, the mixture was filtered to give 3·28 g (34% yield) of (+)-**4** oxalate. The salt was recrystallized from ethanol-ether; m.p. 167–9° (base 78·5–81°); all other spectral data were identical to those of (±)-**4**.

The same general procedure was used to prepare the following:

(−)-N-Hydroxyamphetamine (**4**). From 6·75 g (0·05 mol) of (−)-**1** was obtained 2·76 g (28% yield) of (−)-**4** as the oxalate salt: m.p. 167–9° (base 78·5–81°), all other spectral data were identical with those of (±)-**4**.

(±)-N-*Hydroxyamphetamine* (**4**). From 2·01 g (0·011 mol) of (±)-**1** sulphate was obtained 0·882 g (41% yield) of (±)-**4** as the oxalate: m.p. 167–9° (lit.[11] 175–6°; base 60·5–2°, lit.[11] 63–4°); IR (Nujol) identical to lit.[11]; NMR ($CDCl_3$) δ 1·09 (d, 3, J = 6 Hz, CH_3), 2·73 (m, 2, CH_2); 3·22 (m, 1, CH), 5·77 (broad s, 2, NHOH), 7·24 (m, 5, Ar); mass spectrum *m/e* 152 (0·65), 151 (0·1), 117 (5) 92(12), 91 (27), 65 (9), 60 (100), 45 (10) 42 (15).

(±)-N-*Hydroxynorfenfluramine.* From 7·85 g (0·031 mol) of (±)-norfenfluramine HCl was obtained 1·132 g (11% yield) of (±)-N-hydroxynorfenfluramine as the acid oxalate; m.p. 165·5–7° (lit.[5] 160–161°; base 67–9°); IR (Nujol 1080, 1130, 3160, 3280 cm^{-1} (hydroxylamino); NMR ($CDCl_3$) δ 1·09 (d, 3, J = 6 Hz, CH_3), 2·51–3·53 (m, 3, $CHCH_2$), 6·41 (broad s, 2, NHOH), 7·45 (m, 5, Ar); mass spectrum *m/e* 220 (0·25), 219 (0·05), 159 (22), 109 (8), 60 (100), 46 (10), (13), 42 (22). (Found: C, 46·5; H, 4·4; N, 4·7. Requires: $C_{12}H_{14}F_3NO_5$ (acid oxalate); C, 46·6; H, 4·5; N, 4·5%).

(+)-N-*Hydroxynorfenfluramine.* From 450 mg (1·89 mmol) of (+)-norfenfluramine was obtained 180 mg (18% yield) of (+)-N-hydroxynorfenfluramine as the oxalate: m.p. 177–80° (base 82–5°); spectral data identical to those of (±)-N-hydroxyfenfluramine.

(−)-N-*Hydroxynorfenfluramine.* From 450 mg (1·89 mmol) of (−)-norfenfluramine was obtained 185 mg (18% yield) of (−)-N-hydroxynorfenfluramine as the oxalate: m.p. 177–80° (base 82–5°); spectral data the same as those of (±)-N-hydroxynorfenfluramine.

(±)-N-*Hydroxynorephedrine.* From 6·2 g (0·033 mol) of (±)-norephedrine HCl was obtained 2·7 g (39% yield) of (±)-N-hydroxynorephedrine as the oxalate: m.p. 170–4° dec; IR (neat) 1040, 1135, 3380 cm^{-1} (hydroxylamino), NMR ($CDCl_3$) δ 0·83 (d, 3, J = 6·5 Hz, CH_3), 3·21 (m, 1, CHN), 5·11 (s, 3, OH, NHOH), 5·16 (d, 1, J = 3 Hz, CHOH), 7·30 (s, 5, Ar): mass spectrum *m/e* 168 (1), 167 (1), 108 (12), 107 (12), 105 (9), 79 (20), 77 (20), 60 (100) (Found: C, 56·6; H, 6·7; N, 6·5. Requires: $C_{20}H_{28}N_2O_8$ (oxalate): C, 56·6; H, 6·6; N, 6·6%).

(+)-N-*Hydroxynorpseudoephedrine.* From 6·2 g (0·033 mol) of (+)-norpseudoephedrine HCl was obtained 2·4 g (34% yield) of N-hydroxynorpseudoephedrine as the oxalate: m.p. 144–5°; IR (neat 1030, 1175, 3360 cm^{-1} (hydroxylamino); NMR ($CDCl_3$) δ 0·89 (d, 3, j = 6·5 Hz, CH_3), 3·04 (m, 1, CHN), 4·54 (d, 1, J = 8·4 Hz, CHOH), 5·13 (s, 3, OH, NHOH), 7·28 (s, 5, Ar); mass spectrum *m/e* 168 (1), 167 (1), 118 (14), 117 (15), 108 (23), 107 (24), 105 (16), 79 (44), 77 (45), 60 (100), 51 (16), 44 (23). (Found: C, 56·6; H, 6·6; N, 6·8. Requires: $C_{20}H_{28}N_2O_8$ (oxalate): C, 56·6; H, 6·6; N, 6·6%).

N-*Hydroxyphenylethylamine.* From 5·01 g (0·041 mol) of phenylethylamine was obtained 2·1 g (28% yield) of N-hydroxyphenylethylamine as the oxalate: m.p. 170–75° dec (base 84–5°; lit.[11] 83–4°); IR (Nujol) 1065, 1155, 3180, 3290 cm^{-1} (hydroxylamino); NMR ($CDCl_3$ δ 2·88 (m, 2, $ArCH_2$), 3, 19 (m, 2, CH_2N), 5·90 (s, 2, NHOH) 7·24 (s, 5, Ar); mass spectrum *m/e* 138 (2), 137 (9), 105 (6), 93 (10), 92 (100), 91 (58), 77 (8), 65 (18), 63 (7), 51 (9), 46 (87), 45 (16).

(±)-2-*Hydroxylamino*-1-(2′,6′-*dimethylphenoxy*) *propane.* From 5·0 g (0·0232 mol) of 2-amino-1-(2′,6′)-dimethylphenoxy) propane HCl was obtained 3·1 g (46% yield) of 2 - hydroxylamino - 1 - (2′,6′-dimethylphenoxy) propane as the acid oxalate: m.p. 130·5–1·5° (base 71·5–2·5°); IR (neat) 1030, 1100, 3300 (hydroxylamino), 1215 cm^{-1} (ether); NMR ($CDCl_3$) δ 1·21 (d, 3, J = 6·7 Hz, $CHCH_3$) 2·27 (s, 6, Ar (CH_3)$_2$), 3·43 (m, 1, CH), 3·77 (m, 2, CH_2O), 5·7–6·7 (broad, 2, NHOH), 6·96 (m, 3, Ar); mass spectrum *m/e* 196 (1), 195 (5), 136 (47), 122 (30), 121 (17), 107 (15), 105 (14), 91 (16), 77 (18), 74 (17), 60 (100), 58 (16), 44 (24). (Found: C, 54·5; H, 6·6; N, 5·1; requires: $C_{13}H_{19}NO_6$ (acid oxalate); C, 54·7; H, 6·7; N, 4·9%).

(±)-N-*Hydroxy*-3,4-*dimethoxyamphetamine.* The hydrolysis was conducted as usual with the exception that the reaction media was maintained at 10–15° and the hydrolysis was allowed to proceed for only 1 hr. From 3·92 g (0·02 mol) of 3,4-dimethoxyamphetamine was obtained 0·4 g (7%) of (±)-N-hydroxy-3,4-dimethoxyamphetamine as the oxalate: m.p. 134–136°; (lit.[9] 135–136°). The free base was extracted from a soln (pH = 8) of the oxalate salt and recrystallized from di-isopropylether: m.p. 75–77°; IR (CCl_4) 1043, 1155, 3320 cm^{-1} (hydroxylamino); NMR ($CDCl_3$) δ 1·12 (d, 3, J = 6 Hz, CH_3), 2·35–3·32 (m, 3, $CHCH_2$), 3·85 (s, 6, OCH_3), 6·30 (s, 2, NHOH), 6·79 (s, 3, Ar); mass spectrum *m/e* 211 (10·5), 193 (2·3), 179 (4·7), 151 (100), 150 (40), 137 (46), 121 (9·5), 109 (10), 107 (12), 91 (12), 77 (9), 65 (10), 60 (65), 44 (26), 42 (17). (Found: C, 62·4; H, 8·0; N, 6·4. Requires: $C_{11}H_{17}NO_3$: C, 62·5; H, 8·1; N, 6·6%).

(±) - 2 - *Hydroxylamino* - 1 - (3′ - *trifluromethylthiophenyl*)*propane.* From 966 mg (3·72 mmol) of 2 - amino - 1 -

(3′ - trifluromethylthiophenyl) propane was obtained 77·6 mg of (±) - 2 - hydroxylamino - 1 - (3′ - trifluromethylthiophenyl) propane as the acid oxalate: m.p. 126–130°; mass spectrum *m/e* 252 (1), 251 (1), 208 (25), 191 (10), 139 (21), 138 (9), 91 (16), 90 (10), 89 (8), 78 (6), 77 (7), 65 (7), 61 (8), 60 (100), 46 (23), 45 (40), 44 (23), 42 (25). (Found C, 42·8; H, 4·5; N, 4·1. Requires: $C_{12}H_{24}F_3NO_5S$ (acid oxalate): C, 42·2; H, 4·1; N, 4·1%).

GLC Analysis of the hydroxylamines of amphetamine and norfenfluramine as their trimethylsilyl derivatives. A 3 mg sample of hydroxylamine oxalate was extracted with ether (3 × 3 ml) from a saturated soln of $NaHCO_3$ (2 ml). The ether extracts were combined and dried with $MgSO_4$. Evaporation of the ether with a stream of N_2 gave the hydroxylamines as white solids. The residue was dissolved in 50 μl of MeCN (Dry) and 25 μl of trimethylsilylimidazole was added and the mixture allowed to stand for 5 min. A 2 μl sample was subjected to GLC analysis (System A; N_2 pressure = 15 psi; oven temp. = 90°) and the following retention times were observed: amphetamine, R_t = 3·2 min; TMS derivative of N-hydroxyamphetamine, R_t = 8·8 min; norfenfluramine, R_t = 4·1 min; TMS derivative of N - hydroxynorfenfluramine, R_t = 10·3 min.

General method for the analysis of optical purity of the hydroxylamines

(a) *Derivatization of the hydroxylamines with (−)-TPC.* A 10 mg sample of the hydroxylamine oxalate in satd. $NaHCO_3$ aq. was extracted with ether. The ether extracts were dried with $MgSO_4$ and concentrated under vacuum. The residue was dissolved in 0·2 ml of $CHCl_3$ and 0·4 ml of (−)-TPC reagent (0·1 M in $CHCl_3$) was added. The mixture was allowed to stand at room temp. for 1 hr and a 2–4 ml sample was subjected to GLC analysis (System B).

(b) *Primary hydroxylamines.* A 10 mg sample of the hydroxylamine oxalate in sat. $NaHCO_3$ aq. was extracted with ether and the ether layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was dissolved in 5 ml of Na dried ether and 10 mg of LAH was added. After standing for 2 hr, 2 ml of H_2O was cautiously added and the mixture centrifuged. The ether layer was separated and dried with $MgSO_4$. The ether was removed by boiling in a 40° water bath and 100 μl of (−)-TPC reagent (0·1 M in CH_3Cl) was added to the residue. A 2–4 μl sample was subjected to GLC analysis (System B). The peak height ratio (peak height of the small peak ÷ peak height of the large peak) was compared to that obtained from a GLC analysis (System B) of the (−)-TPC derivative of the amine used in the preparation of the hydroxylamine.

(c) *Secondary hydroxylamines.* A 10 mg sample of the hydroxylamine oxalate was dissolved or suspended in 5 ml of H_2O and 1 ml of titanous chloride soln (12·5%, Hopkins & Williams Ltd). The mixture was allowed to stand for 18 hr in the dark and 1 ml of 20% NaOH was added. The resulting mixture was extracted with 2 × 4 ml of ether. The ether extracts were pooled and dried with $MgSO_4$. The ether was evaporated (40° water bath) and 100 μl of (−)-TPC reagent was added. A 2–4 μl sample was analysed by GLC and the peak height ratio was compared to that of the (−)-TPC derivative of the amine used for the preparation of the hydroxylamine.

Acknowledgements—One of us (K.H.) thanks the Medical Research Council of Canada and another (P.H.M.) thanks the medical Research Council of Great Britain for post-doctoral fellowships while G.R.J. thanks the Pharmaceutical Society of Great Britain for a research scholarship.

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