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# THE ABSOLUTE CONFIGURATION OF (+)-1-(3-TRIFLUOROMETHYLPHENYL)-2-ETHYLAMINO PROPANE [(+)-FENFLURAMINE]

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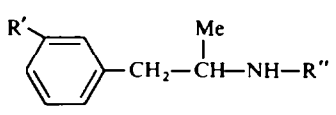
**Abstract**—The absolute configuration of (+)-fenfluramine [(+)-1-(3-trifluoromethylphenyl) 2-ethylaminopropane] and of (+)-norfenfluramine [(+)-1-(3-trifluoromethylphenyl) 2-aminopropane] has been shown to be identical to that of (+)-amphetamine and (+)-methyl amphetamine (the S-configuration) by the similarity of the ORD and CD curves of the appropriate N-nitroso and N-salicylidene derivatives of these compounds.

(+)-FENFLURAMINE* [(+)-1-(3-trifluoromethylphenyl) 2-ethylaminopropane](Ia) is a new, non-stimulant anorectic agent[1] chemically related to (+)-amphetamine [S-(+)-α-methyl-β-phenyl ethylamine] (Ib) and (+)-methylamphetamine (Ic) which are stimulant anorectic agents. On oral administration to humans (+)-fenfluramine is de-ethylated to norfenfluramine (Id).[2] The anorectic activity of (±)-amphetamine lies mainly in the (+)-isomer[3,4] (Ib) which has the same configuration as (+)-methylamphetamine (Ic).[5] The N-acetyl derivatives of (+)-amphetamine (Ib)[6,7]



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(a) R′ = $CF_3$; R″ = Et
(b) R′ = H; R″ = H
(c) R′ = H; R″ = Me
(d) R′ = $CF_3$; R″ = H
(e) R′ = H; R″ = Et

and of (+)-norfenfluramine (Id) which gave plain negative ORD curves in methanol were reduced with LAH to give (+)-ethylamphetamine (Ie)[6] and (+)-fenfluramine (Ia) respectively, of the same configuration as the starting compounds Ib and Id. These compounds, Ia and Ie, gave plain positive ORD curves in 95% ethanol.

Identical configuration for (+)-amphetamine and (+)-fenfluramine is thus indicated since ring substitution is known to have little effect on the sign of optical rotation.[8] The configurational relationship between (+)-fenfluramine and (+)-norfenfluramine and (+)-amphetamine and (+)-methylamphetamine was established unequivocably by examination of ORD and CD curves of the N-nitroso derivatives of the above secondary amines and the N-acetyl and N-salicylidene derivatives of the above primary amines.

N-*Nitrosoamine derivatives.*[9–12] The N-nitrosoamine derivatives of (+)-ethylamphetamine (Ie), (+)-fenfluramine (Ia) and (+)-methylamphetamine (Ic) gave similar ORD and CD curves in iso-octane (Fig. 1) the Cotton effects occurring in the

* (±)-Fenfluramine marketed as Ponderax by Selpharm Laboratories Limited (London).

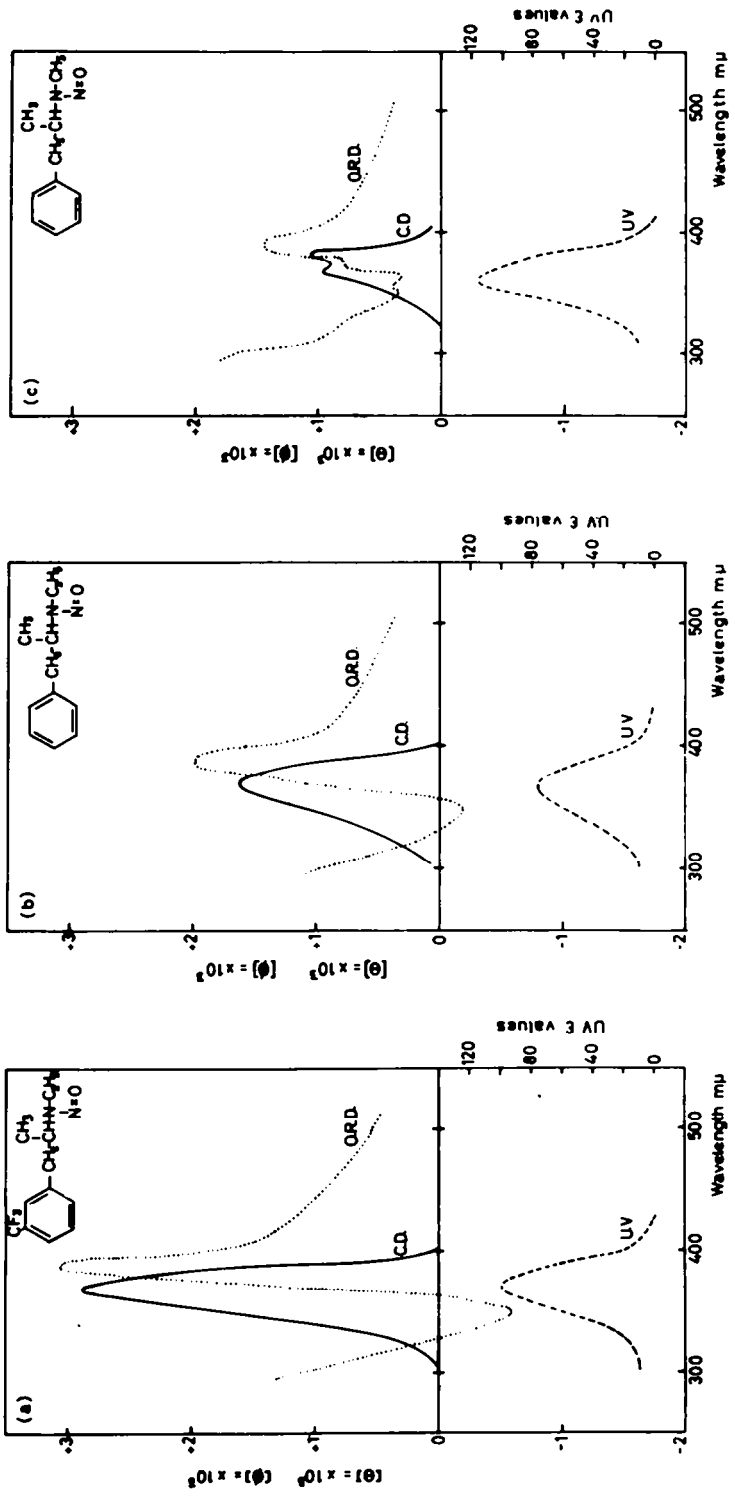


FIG. 1. ORD CD and UV spectra of the N-nitroso derivatives of: (a) (+)-fenfluramine, (b) (+)-ethylamphetamine and (c) (+)-methylamphetamine, in iso-octane.

expected region, 330–370 mμ.[9–15] Overberger *et al.*[12] has shown that such N-nitrosation occurs without racemization. The change from N-ethyl to N-methyl in these compounds produces asymmetry in the ORD and CD curves; this is a true effect since the N-nitroso amine derivatives of (−)-ethyl and (−)-methylamphetamine gave mirror image curves of those presented in Fig. 1.

N-*Nitrosoacetamide derivatives.* The N-nitrosoacetamide derivative of (+)-norfenfluramine (Id) and (+)-amphetamine (Ib) were prepared from their corresponding acetyl compounds according to the method of White.[9,16,17] In iso-octane these compounds have identical ORD and CD curves (see also La Manna *et al.*[17] for ORD curve of N-nitrosoacetamide derivative of Ib).

N-*Salicylidene derivatives.*[18–20] The N-salicylidene derivatives of (+)-amphetamine (Ib) and (+)-norfenfluramine (Id), prepared according to Velluz *et al.*,[20] in isooctane gave almost identical ORD and CD curves and Cotton Effects with maxima at 332 mμ and 265–263 mμ.

The above results establish that (+)-fenfluramine and its de-ethylated metabolite (+)-norfenfluramine have the same absolute configuration as (+)-amphetamine, i.e. the S-configuration.[8,21,22,27]

## EXPERIMENTAL

*Circular dichroism measurements.* CD measurements were made using a Roussel-Jouan Dichrograph operating with concentrations such that the slit width was no greater than 1·2 mm at the CD maxima, and an instrument sensitivity setting of 1·5. The cell path length was 2 cm. Molecular ellipticity was calculated as $[\theta] = 3300\,\Delta\varepsilon$, with $\Delta\varepsilon = \Delta D c^{-1} l^{-1}$.

*Optical rotation measurements.* ORD measurements were made using a Bellingham Stanley/Bendix-Ericsson Polarimatic 62 equipped with a 250 W Supersil Xenon lamp with constant $N_2$ purging (1·0 cm cell, range 150 mm = 50,200 or 500 millidegrees for salicylidene, nitrosoacetamide and nitrosoamine derivatives respectively). Molecular rotation $[\phi]$ was calculated as $[\phi] = 10\,\alpha.\text{mol wt}\; l^{-1}c^{-1}$ where $\alpha$ is sensitivity in millidegrees.

UV spectra were obtained using a Unicam SP 800 spectrophotometer and IR spectra using a Unicam SP 100 spectrophotometer on liquid films or Nujol mulls. M.p. values are uncorrected.

*Thin-layer chromatography.* Glass plates, 20 × 20 cm, covered with silica gel G (Merck) 0·25 mm thick, prepared according to Stahl[23] were used, and solvents run at room temp (ca. 24°). Systems:

(A) MeOH–$CHCl_3$, 20:80
(B) MeOH–Acetone, 50:50
(C) MeOH–Acetone–(Triethanolamine), 50:50(5 drops)
(D) MeOH–$CHCl_3$–[Ammonia (880)], 10:90[5 drops]

All compounds were visualized by spraying with Dragendorff's Reagent.[24] All oils (described later) were examined by TLC in the above 4 systems and shown to give only one spot. IR spectra and GLC techniques also showed the absence of precursors and reagents. Physical measurements were made on the N-nitroso derivatives immediately after preparation; distillation led to decomposition.[9]

N-*Acetyl derivative of* (+)-1-(3-*trifluoromethylphenyl*) 2-*aminopropane* (Id). The method used was the same as that for the preparation of the N-acetyl derivative of (+)-amphetamine but using Id[25] (0·41 g; 2·02 m mole) in place of (+)-amphetamine. The resultant solid was washed with water, dried and sublimed (0·40 g; 1·64 m mole) m.p. 75·5–78°, $[\alpha]_D^{22.5}$ −32·5° (*c*, 2·0 in $CHCl_3$); $\nu_{max}^{Nujol}$ 3300, 1644 $cm^{-1}$. (Found: C, 59·2; H, 5·8; N, 5·9. $C_{12}H_{14}NOF_3$ requires: C, 58·8; H, 5·7; N, 5·7%.)

N-*Acetyl derivative of* (+)-*amphetamine.* The method used was similar to that described by Welsh,[6,7] using a cold suspension of Ib (0·27 g; 2·0 mmole) in an aqueous soln (10 ml) of $Na_2CO_3$ (0·42 g; 5·0 mmole) to which $Ac_2O$ (0·30 g; 3·0 mmole) was added with shaking. The solid which separated was washed with water, dried and sublimed to give N-acetyl-amphetamine (0·30 g; 1·7 mmole) m.p. 122·5–124°. Leonard *et al.*[6] give m.p. 121–124°; Welsh[7] gives m.p. 124°; $[\alpha]_D^{21.5}$ -44·25°(*c*, 2·0 in $CHCl_3$); $\nu_{max}^{Nujol}$ 3250, 1644 $cm^{-1}$.

Leonard *et al.*[6] give $[\alpha]_D^{25}$-43·5° (*c*, 2·0 in $CHCl_3$); $\nu_{max}^{Nujol}$ 3215, 1644 $cm^{-1}$; Welsh[7] gives $[\alpha]_D^{25}$-44° (*c*, 2·0 in $CHCl_3$).

(+)-1-(3-*Trifluoromethylphenyl*) 2-*ethylaminopropane* (Ia). To a stirred mixture of dry THF (8 ml) and LAH (0·23 g; 6·0 mmole) was added a soln of the N-acetyl derivative of Id (0·98 g; 4·0 mmole) in dry THF (8 ml), over a period of 10 min. The whole was refluxed with stirring for 16 hr, after which Ia (0·7 g; 3·0 mmole) was isolated in the usual manner and purified by repeated extractions. The identity of this compound was established to be the same as that of an authentic sample of (+)-fenfluramine[1] using UV, IR and GLC techniques together with ORD examinations of the free base and of its N-nitrosoamine derivative. TLC in systems A,B,C and D gave one spot with respective $R_f$ values of 0·9, 0·26, 0·24 and 0·62.

(+)-*Ethylamphetamine*. The method used was the same as that for the preparation of Ia but using the N-acetyl derivative of (+)-amphetamine (0·65 g; 4·0 mmole) in place of the N-acetyl derivative of Id. The resultant liquid gave characteristics identical to those reported by Leonard *et al.*;[6] $[\alpha]_D^{29}$ 36° (*c*, 10·0 in 95% EtOH); $n_D^{25}$ 1·4986.

N-*Nitrosoamine derivatives of* (+)-*ethylamphetamine*, (+)-*methylamphetamine and* (+)-1-(3-*trifluoromethylphenyl*) 2-*ethylaminopropane and the corresponding* (−)-*isomers*. Two solns were prepared, one containing the secondary amine (0·4–0·5 g) in water (4 ml), the other containing $NaNO_2$ (0·3–0·4 g) in water (1 ml). both solns being cooled to 4°. Conc HCl (1 ml) was added to the amine solns, shaken and the $NaNO_2$ aq added rapidly, with shaking. After 10 min the mixture was extracted with ether (10 ml) and the ethereal layer washed successively with water, 5% $Na_2CO_3$ aq and water, to remove all traces of nitrous acid. The ethereal soln was dried over $Na_2SO_4$ and the solvent removed under vacuum. All derivatives were colourless oils.

N-*Nitrosoamine derivative of* (+)-1-(3-*trifluoromethylphenyl*) 2-*ethylamine propane* (Ia). $n_D^{21}$ 1·4759; $R_f$ values in systems A, B, C and D were respectively 0·82, 0·85, 0·87 and 0·86; ORD data; concentration, 1 mg/ml iso-octane; cell path length, 1 cm, t, −1·5°. $[\phi]_{500}$ = +563·6°, $[\phi]_{417}$ = +1343·9°, $[\phi]_{389}$ = +3077·9° $[\phi]_{370}$ = +1040·4°, $[\phi]_{364}$ = 0°, $[\phi]_{351·5}$ = −606·9°, $[\phi]_{327·5}$ = 0°, $[\phi]_{313}$ = +650·3°, $[\phi]_{303}$ = 1170·5. CD data; concentration 1 mg/ml iso-octane; cell path length, 2 cm; t, 25°; $[\theta]_{400}$ = 32·18, $[\theta]_{390}$ = 1608·8, $[\theta]_{385}$ = 2252·3, $[\theta]_{380}$ = 2413·1, $[\theta]_{370}$ = 2831·4, $[\theta]_{350}$ = 1480·1, $[\theta]_{330}$ = 386·1, $[\theta]_{310}$ = 32·2.

N-*Nitrosoamine derivative of* (+)-*ethylamphetamine*. $n_D^{21}$ 1·5145; $R_f$ values in systems A, B, C and D were respectively 0·82, 0·81, 0·88 and 0·89; ORD data; concentration, 1·28 mg/ml iso-octane; cell path length, 1 cm; t, −1·5°; $[\phi]_{500}$ = 387·5°, $[\phi]_{417}$ = +900°, $[\phi]_{389}$ = +2000°, $[\phi]_{370}$ = +800°, $[\phi]_{357}$ = 0°, $[\phi]_{351·5}$ = −200°, $[\phi]_{333}$ = 0°, $[\phi]_{313}$ = +575°, $[\phi]_{303}$ = +975°. CD data; concentration, 1·28 mg/ml iso-octane; cell path length, 2 cm; t, 25°; $[\theta]_{400}$ = 37·1, $[\theta]_{390}$ = 761·2, $[\theta]_{385}$ = 1225·3, $[\theta]_{380}$ = 1373·8, $[\theta]_{370}$ = 1615·2, $[\theta]_{350}$ = 1132·5, $[\theta]_{330}$ = 519·8, $[\theta]_{310}$ = 130.

N-*Nitrosoamine derivative of* (+)-*methylamphetamine*. $n_D^{21}$ 1·5330, $R_f$ values in systems, A, B, C and D were respectively 0·8, 0·75, 0·84 and 0·83; ORD data; concentration, 0·93 mg/ml iso-octane; cell path length, 1 cm, t, −1·5°; $[\phi]_{500}$ = +398·8°, $[\phi]_{417}$ = +797·5°, $[\phi]_{389}$ = +1467·4°, $[\phi]_{372·3-378}$ = +784·7°, $[\phi]_{363·5}$ = 319°, $[\phi]_{355·5}$ = +382·8°, $[\phi]_{349·5}$ = +350·9°, $[\phi]_{333}$ = +701·8°, $[\phi]_{313}$ = +988·9°, $[\phi]_{303}$ = +1629·9°; CD data; concentration, 0·93 mg/ml iso-octane; cell path length, 2 cm; t, 25°; $[\theta]_{400}$ = 118·3, $[\theta]_{390}$ = 378·4, $[\theta]_{382}$ = 1052·4, $[\theta]_{375}$ = 875·1, $[\theta]_{367}$ = 946, $[\theta]_{350}$ = 378·4, $[\theta]_{330}$ = 71·0.

N-*Nitrosoacetamides of* (+)-*amphetamine and* (+)-1-(3-*trifluoromethyl phenyl*) 2-*aminopropane*. The general method used by White[16] was adopted. A soln of Ib or Id (approx 0·2 g; 0·80 mmole) in a mixture of AcOH (1·15 ml) and $Ac_2O$ (5·65 ml) was cooled to 0° and $NaNO_2$ (1·77 g; 0·026) was added during ca·5 hr. After 10–14 hr (overnight period) at 0°, the temp was allowed to rise to 10–15° (during ca. 30 min) and this mixture poured into an ice/water mixture. The N-nitrosoacetamide derivative was extracted with ether and the ethereal phase washed successively with water, an aqueous soln of 5% $Na_2CO_3$ aq, water, and finally dried with $Na_2SO_4$. The solvent was removed under reduced press and the resultant yellow oil kept in a refrigerator prior to examination.

N-*Nitrosoacetamide derivatives of* (+)-*amphetamine*. ORD data; concentration, 720 μg/ml iso-octane; cell path length, 1 cm; t, −1·5°; $[\phi]_{451}$ = −839·3°, $[\phi]_{433}$ = −2365·3°, $[\phi]_{418}$ = +496·0°, $[\phi]_{409}$ = −76·3°, $[\phi]_{395}$ = +1526°, $[\phi]_{388}$ = +1335·3°, $[\phi]_{380}$ = +1640·5°; CD data; concentration, 720 μg/ml iso-octane; cell path length, 2 cm; t, 25°; $[\theta]_{445}$ = −247·8, $[\theta]_{437·5}$ = −35·4, $[\theta]_{430}$ = −1380·6, $[\theta]_{424}$ = −2761·2, $[\theta]_{412·5}$ = −1345·2, $[\theta]_{405}$ = −2265·6, $[\theta]_{393}$ = −1132·8, $[\theta]_{389}$ = −1168·2.

N-*Nitrosoacetamide derivative of* (+)-*norfenfluramine*. ORD data; concentration, 1·053 mg/ml iso-octane; cell path length, 1 cm; t, −1·5°; $[\phi]_{448}$ = −469·8°, $[\phi]_{431}$ = −1287·6°, $[\phi]_{420}$ = +226·2°,

$[\phi]_{412} = -87{\cdot}0°$; $[\phi]_{396} = +765{\cdot}6°$, $[\phi]_{379} = +835{\cdot}2°$; CD data; concentration, 1·053 mg/ml iso-octane; cell path length, 2 cm; t, 25°. $[\theta]_{445} = -64{\cdot}6$, $[\theta]_{437{\cdot}5} = 0$, $[\theta]_{430} = -1194{\cdot}0$, $[\theta]_{425{\cdot}5} = -1807{\cdot}4$, $[\theta]_{413{\cdot}5} = -710{\cdot}0$, $[\theta]_{405} = -1420{\cdot}1$, $[\theta]_{395} = -645{\cdot}5$, $[\theta]_{390} = -677{\cdot}8$.

*N-Salicylidene derivative of (+)-amphetamine.* (+)-Amphetamine (0·1 g; 0·74 mmole) was dissolved in MeOH (2 ml) and salicylaldehyde (0·125 ml) added. The mixture was put into a refrigerator for 10 days until the N-salicylidene derivative of (+)-amphetamine (0·15 g; 0·63 mmole) crystallized out.[20] The crystals, separated by centrifugation and washed with pet. ether 40/60 to remove traces of salicylaldehyde, had m.p. 58·5°, $[\alpha]_D^{24}$ +349° (*c*, 1·0 in abs. alcohol). Smith *et al.*[26] give m.p. 58–60° and $[\alpha]_D^{24}$ +346° (*c*, 1·0 in abs. alcohol); ORD data; concentration 36·7 μg/ml iso-octane; cell path length, 1 cm; t, 22·5°; $[\phi]_{385} = +4774°$, $[\phi]_{331{\cdot}5} = +13{,}454°$, $[\phi]_{318} = +5859°$, $[\phi]_{296} = -5642°$, $[\phi]_{270} = +7595°$, $[\phi]_{263} = +16{,}275°$, $[\phi]_{256} = +6510°$; CD data; concentration 36·7 μg/ml iso-octane; cell path length, 2 cm, t, 22·5°; $[\theta]_{350} = 1208$, $[\theta]_{340} = 3223$, $[\theta]_{330} = 8864$, $[\theta]_{320} = 14{,}506$, $[\theta]_{310} = 14{,}506$, $[\theta]_{300} = 9670$, $[\theta]_{290} = 4029$, $[\theta]_{280} = 1611$.

*N-Salicylidene derivative of (+)-1-(3-trifluoromethylphenyl) 2-aminopropane.* Equimolar proportions (0·75 mmole) of (+)-norfenfluramine and salicylaldehyde were mixed, the liberated water being removed by placing the preparation in an evacuated desiccator over $P_2O_5$ and silica gel. The resultant yellow oil gave one spot on TLC in systems A, B, C and D with respective $R_f$ values of 0·84, 0·85, 0·94 and 0·89, $n_D^{21}$ 1·5379. (Found: C, 66·9; H, 5·62; N, 5·7. $C_{17}H_{16}NOF$ requires: C, 66·4; H, 5·2; N, 4·6%); ORD data; concentration, 33·8 μg/ml; iso-octane call path length, 1 cm; t, 22·5°; $[\phi]_{385} = +3349°$, $[\phi]_{331{\cdot}5} = +13550°$, $[\phi]_{318} = +3654°$, $]\phi]_{301} = -5786°$, $[\phi]_{270} = -7917$, $[\phi]_{265} = +15834°$, $[\phi]_{256} = +3045°$; CD data; concentration, 33·8 μg/ml iso-octane; cell path length, 2 cm; t, 22·5°; $[\theta]_{350} = 1686$, $[\theta]_{340} = 4496$, $[\phi]_{330} = 12{,}364$, $[\theta]_{320} = 16{,}298$, $[\theta]_{310} = 15{,}736$, $[\theta]_{300} = 8992$, $[\theta]_{290} = 4496$, $[\theta]_{280} = 2248$.

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