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THE HIGHLY STEREOSELECTIVE CONVERSION OF N,N-DIMETHYLAMPHETAMINE INTO N-METHYLPSEUDOEPHEDRINE; A MIMIC OF THE ENZYME MEDIATED STEREOSPECIFIC BENZYLIC HYDROXYLATION OF 2-ARYLETHYLAMINES.

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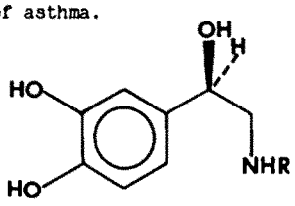
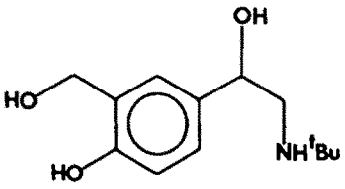
Summary - Treatment of (S)-(η^6-N,N-dimethylamphetamine)Cr(CO)$_3$ with n-butyllithium below -40°C gives a stable benzylic carbanion via loss of the pro-R-benzylic proton. Warming of this anion above -40°C gives (η^6-E-β-methylstyrene)Cr(CO)$_3$ via an ElcB type elimination whilst trapping with an electrophile below -40°C gives benzylically functionalised amphetamines with overall retention of configuration. The use of oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide as the electrophile gives optically pure (1S,2S)-N-methylpseudoephedrine after decomplexation.

A number of compounds which possess either α- or β-adrenergic activity contain the β-amino-alcohol moiety. Representatives of this class include the natural catecholamines, adrenaline (1), noradrenaline (2), and the potent β-agonist Salbutamol (3)[2] used in the treatment of asthma.





1 R = Me 2 R = H

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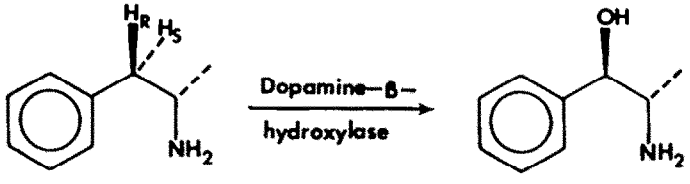
Whilst many pharmaceuticals are still produced in racemic form there is a growing appreciation of the different biological effects of enantiomeric molecules and as a result the preparation of optically pure β-amino-alchols has attracted condiserable attention.[3]

The in vivo production of optically pure 2-arylethanolamines from 2-arylethylamines is catalysed by dopamine β-hydroxylase, a copper containing mono-oxygenase.[4]. For example, the conversion of (S)-amphetamine (4) into (1R, 2S)-norephedrine (5) is catalysed by dopamine-β-hydroxylase and occurs with concomitant loss of the pro-R-hydrogen atom from the benzylic position and overall retention of stereochemistry.[5]



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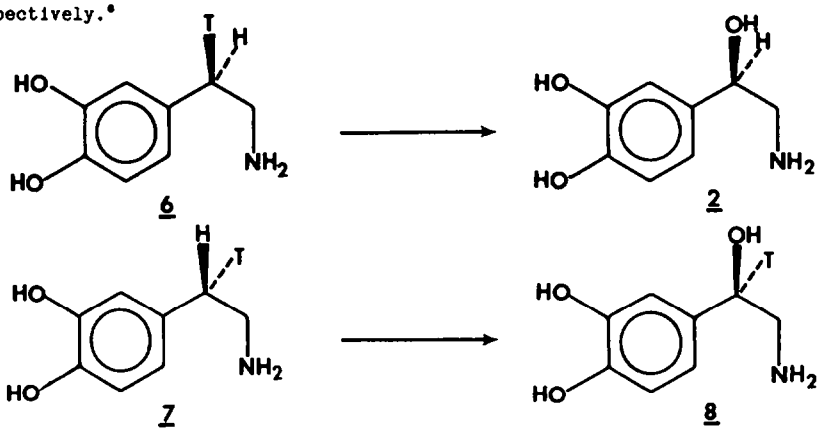
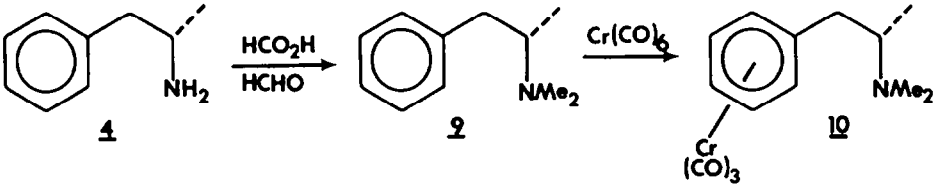
A similar reaction occurs with retention of configuration in the conversion of (2R) or (2S)-2[$^3H_1$]-dopamines (6) or (7) to noradrenalin (2) or (8) with loss of tritium atom or a proton respectively.[6]



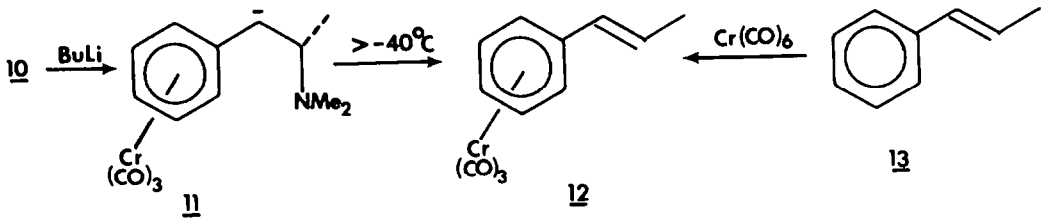
All previous attempts to mimic these enzyme mediated reactions via the formation of a benzylic carbanion have failed due to elimination of the β-amino function with formation of styrenes.[7] We have previously reported the facile stereoselective benzylic functionalisation of tetrahydroisoquinolines[8] and of the protoberberine alkaloid canadine[9] via coordination to the chromium tricarbonyl unit. We report here the extension of this methodology to N,N-dimethylamphetamine. Highly stereoselective benzylic functionalisation is achieved via the formation of a chromium tricarbonyl stabilised benzylic carbanion. Part of this work has been the subject of a preliminary communication.[10]

Results and Discussion

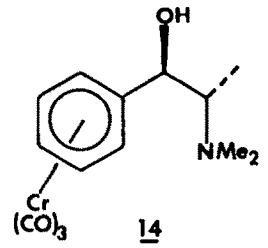
(S)-(+)-Amphetamine (4) was treated with formaldehyde and formic acid to give (S)-(+)-N,N-dimethylamphetamine (9) (64%).[11] Thermolysis of hexacarbonyl chromium in a 10:1 mixture of di-n-butyl ether and tetrahydrofuran containing (S)-(+)-N,N-dimethylamphetamine (9) give (S)-(-)-(N,N-dimethylamphetamine)Cr(CO)$_3$ (10) as yellow needles (70%) after crystallisation.



Treatment of a THF solution of complex (10) at -78°C with n-butyllithium gave the characteristic incarnidine colour of a chromium tricarbonyl stabilised benzylic carbanion. This anion was stable at low temperature but at -40°C, or above, elimination of the dimethylamino moiety occurred. For example, stirring a THF solution of the anion (11) (2h, -40°C) followed by the addition of methanol gave (E-β-methylstyrene)Cr(CO)$_3$ (12) identical in all respects with an authentic sample prepared by thermolysis of hexacarbonyl chromium in di-n-butyl ether and THF containing E-β-methylstyrene (13).



Treatment of a THF solution of the anion (11) at -78°C with MoOPH[12] effected an oxidation to the corresponding benzylic alcohol (35% yield). In principle either or both of the diastereoisomers (1S, 2S)-(N-methylephedrine)Cr(CO)$_3$ (14) or (1R,2S)-(N-methylpseudophedrine) Cr(CO)$_3$ (15) could be obtained. In order to facilitate analysis of the reaction product, complexes (14) and (15) were prepared via an alternative route.



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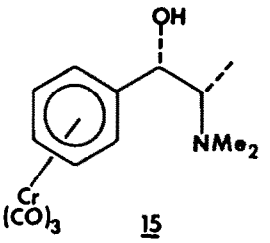

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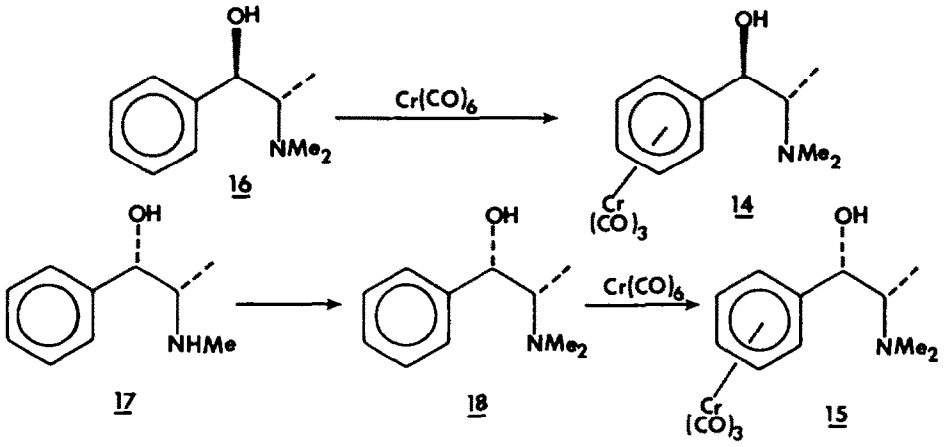
An authentic sample of (1S, 2S)-(N-methylephedrine)Cr(CO)$_3$ (14) {$[\alpha]_D^{\circ}$-22.2° (C, 1.5 in $CHCl_3$)} was prepared by complexation of commercially available (1R, 2S)-(-)-N-methylephedrine (16).[13] † The most efficient complexation (48% yield) was obtained by terminating the reaction after eight hours. An authentic sample of (1R, 2S)-(N-methylpseudoephedrine)Cr(CO)$_3$ (15) {$[\alpha]_D^{\circ}$ -30.0° (C, 0.15 in $CHCl_3$)} was prepared from commercially available (1S, 2S)-(+)-pseudo-ephedrine (17).[13] Treatment of (17) with formaldehyde and formic acid gave (1S, 2S)-(+)-N-methylpseudoephedrine (18).[14] Complexation of (18) to the Cr(CO)$_3$ moiety was achieved in poor yield (3%) by thermolysis of hexacarbonyl chromium in di-n-butyl ether and THF containing (18) for eight hours. The yields of compelxation of these 2-arylethanolamine systems may be much improved by their conversion to O-methyl ethers.[15]

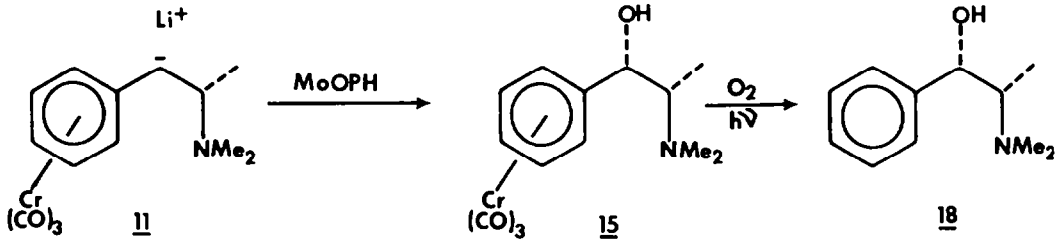


16 14 17 18 15

Analysis of the ^{1}H n.m.r. spectrum of the MoOPH oxidation product of the anion (11) indicated that a single diastereoisomer had been formed which was identical in all respects with an authentic sample of (1R, 2S)-(N-methylpseudoephedrine)Cr(CO)$_3$ (15) including an optical rotation {$[\alpha]_D^{\circ}$ - 31° (c, 0.25 in $CHCl_3$)}. The product was clearly different from (1S, 2S)-(N-methyl ephedrine)Cr(CO)$_3$ (14) none of which could be detected in the crude reaction mixture.

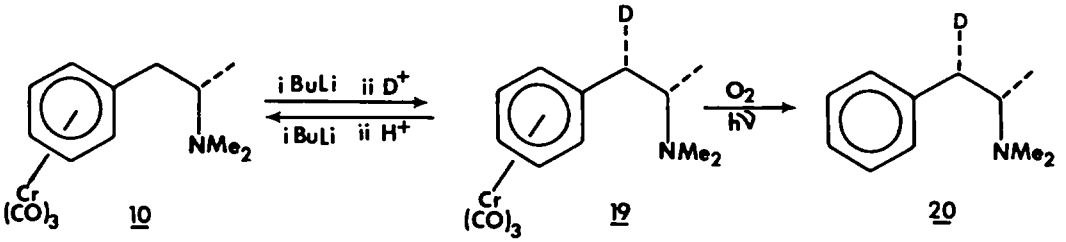
† The (R)-absolute configuration at the α-centre of compound (16) becomes (S) on complexation to the Cr(CO)$_3$ moiety by definition.

Decomplexation of the MOOPH oxidation product by allowing a diethyl ether solution of the product to stand in air and sunlight until colourless gave (1S, 2S)-N-methylpseudophedrine (18) identical in all respects with an authentic sample and clearly different from an authentic sample of (1R, 2S)-N-methylephedrine (16).

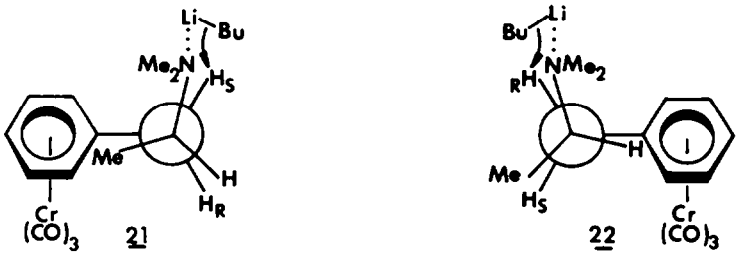


Treatment of a solution of the anion (11) at -78°C with d¹-methanol gave the benzylically deuterated complex (19). ^{1}H n.m.r. spectroscopy and mass spectrometry indicated essentially complete monodeuterium incorporation. Only a single diastereoisomer could be detected by 300 MHz ^{1}H and 38.4 MHz ^{2}H n.m.r. spectroscopy and, by analogy with the MoOPH oxidation reaction, the product was assigned as (1S, 2R)-[(2-^{2}H)-N,N-dimethylamphetamine]Cr(CO)$_3$ (19). Decomplexation gave (1S, 2S)-(2-^{2}H)-N,N-dimethylamphetamine (20).

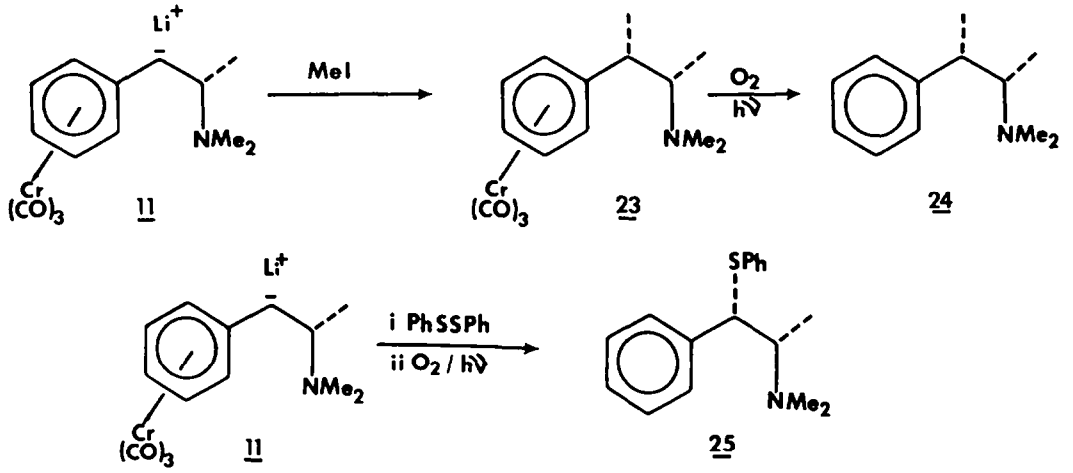
The reaction of a THF solution of complex (19) sequentially at -78°C with n-butyllithium and methanol regenerated the parent complex (10). ^{2}H n.m.r. spectroscopy revealed no deuterium indicative of a highly stereoselective abstraction of deuterium since it overcomes the unfavourable kinetic isotope effect. Moreover, the regenerated complex (10) exhibited an optical rotation {$[\alpha]_D^{20}$ -26.5° (c, 0.1 in $CHCl_3$)} identical with that of an authentic sample. These results show that no racemisation at the β-carbon was occurring via an elimination/addition mechanism involving the anion (11) and that it is the pro-R hydrogen from complex (10) that is stereoselectively abstracted.



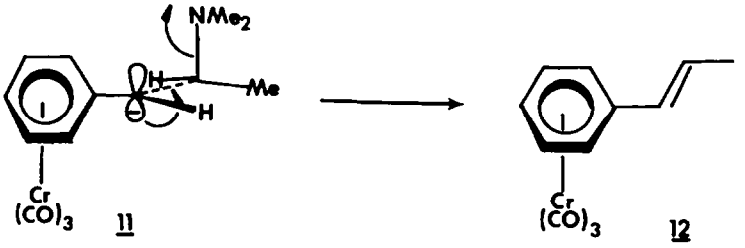
The results presented above demonstrate the highly stereoselective removal of the benzylic pro-R-hydrogen of (N,N-dimethylamphetamine)Cr(CO)$_3$ (10) and subsequent oxidation or deuteration with retention of configuration. We propose that the highly stereoselective removal of the pro-R-benzylic hydrogen arises from chelation of the n-butyllithium to the nitrogen lone pair of complex (10). Assuming this to be the case then in all transition states leading to removal of the pro-S-hydrogen (21) an unfavourable eclipsing interaction exists between the β-methyl group and the bulky phenyl chromium tricarbonyl moiety. On the other hand all transition states leading to the removal of the pro-R-hydrogen (22) avoid this interaction.



The anion (11) was also trapped by methyl iodide to give (1S, 2R) -(N,N-dimethyl-2-methylamphetamine)Cr(CO)$_3$ (23) {[α]$_D^{\circ}$ - 20.2° (c, 0.45 in CHCl$_3$)} which was decomplexed to give (1S, 2S)-N,N-dimethyl-2-methylamphetamine (24) {[α]$_D^{\circ}$ + 15.6° (c, 0.43 in CHCl$_3$)}. Treatment of the anion (11) with phenyl disulphide followed by decomplexation gave (1S, 2S)-N,N-dimethyl-1-thiophenylamphetamine (25) {[α]$_D^{\circ}$ + 343.7° (c, 0.6 in CHCl$_3$)}.



The exclusive formation of (E-β-methylstyrene)Cr(CO)$_3$ on warming a THF solution of the anion (11) above -40°C is consistent with an overall syn-elimination via an ElcB type mechanism. Removal of the pro-R-hydrogen from (N,N-dimethylamphetamine)Cr(CO)$_3$ (10) as described above gives the stabilsed carbanion (11) which, on warming, loses the dimethylamino moiety from the exo-face to give the more stable trans-alkene.



Conclusions:

The highly stereoselective benzylic functionalisation of (S)-(-)-(N,N-dimethylamphetamine) Cr(CO)$_3$ (10) has been demonstrated via n-butyllithium mediated removal of the pro-R-benzylic proton. The use of MoOPH as the electrophile gives (1S,2S)-N-methylpseudoephedrine (18) after decomplexation. This methodology represents the only chemical mimic of the enzymatic hydroxylation of 2-arylethylamines to optically pure 2-arylethanolamines.

Experimental

All reactions involving the preparation and utilisation of (arene)Cr(CO)$_3$ complexes were performed under an atmosphere of nitrogen using standard vacuumn line and Schlenk techniques[17], unless otherwise stated. Removal of all solvents was performed under reduced pressure. All commercial reagents were purified according to standard procedure.[18] THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. Diethyl ether was peroxide free and di-n-butyl ether was dried over sodium and distilled under nitrogen before use. Petroleum ether refers to that fraction boiling between 40 and 60°C whilst hexane refers to that fraction of petroleum ether boiling between 67 and 70°C.

n-Butyllithium was used as a 1.6M solution in hexane. Hexacarbonyl chromium was steam distilled prior to use and stored under nitrogen. Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) was prepared according to the method of Mimoun.[12,19]

Flash chromatgraphy was performed on SiO_2 (Merck, 40-40μm) under a positive nitrogen pressure. Infrared spectra were obtained as solutions in chloroform unless otherwise stated and ^1H n.m.r. spectra were obtained at 300MHz in d^1-chloroform unless otherwise stated. ^2H n.m.r.spectra were obtained at 38.4MHz as solutions in chloroform containign d^1-chloroform as an internal standard. Mass spectra were recorded on a V.G. micromass ZAB IF or MM 30F instrument using In Beam Electron Impact techniques unless otherwise stated. Optical rotations were performed on a Perkin-Elmer 241 polarimeter.

(S)-(+)-N,N-Dimethylamphetamine (9).[11]

D-Amphetamine sulphate (9.00 g, 24.47 mmol) was dissolved in 1M sodium hydroxide solution (50 ml). Extraction with diethyl ether (3 x 50 ml), drying ($MgSO_4$) and evaporation gave S-amphetamine (4) (5.54 g, 41.04 mmol). This was heated with formaldehyde (8.3 ml, 37% aqueous solution, 109.8 mmol) and formic acid (5 ml, 98% aqueous solution, 129.9 mmol) (100°C, 8 h). The cooled solution was basified (2M NaOH), extracted with diethyl ether (3 x 100 ml), dried ($MgSO_4$) and evaporated to a yellow oil. Distillation (b.p. 58°C at 0.1 mm Hg) gave the title compound as a colourless liquid (4.25 g, 63.5%); ν_{max} 2795 ($N(CH_3)_2$) cm^{-1}; δ_H 7.31 - 7.17 (m, 5H, ArH), 2.97, 2.41 (AB part of ABX system, J_{AB} = 12.9 Hz, J_{AX} = 4.0 Hz, J_{BX} = 5.6 Hz, 2H, $ArCH_2R$), 2.85 - 2.78 (m, 1H, $RCH(CH_3)N(CH_3)_2$), 2.35 (s, 6H, $RN(CH_3)_2$), 0.93 (d, J = 6.6 Hz, $RCH(CH_3)N(CH_3)_2$); m/z = 135(M^+); $[\alpha]_D^{20}$ + 3.6° (c, 0.8 in $CHCl_3$); [Lit[20] $[\alpha]_D$ + 3.4° (neat)].

(S)-(-)-(η^6-N,N-Dimethylamphetamine)tricarbonylchromium(0) (10)

A deoxygenated mixture of di-n-butyl ether (75 ml), THF (7.5 ml), (S)-(+)-N,N-dimethylamphetamine (9) (2.00 g, 12.27 mmol) and hexacarbonyl chromium (4.10 g, 18.64 mmol) was heated at reflux (24 h). The cooled solution was filtered and the solvents removed. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/petroleum ether then Et_2O) gave a yellow solid. Crystallisation (Et_2O/hexane) gave the title compound as fine yellow needles (2.55 g, 69.5%); ν_{max} 2795 ($N(CH_3)_2$), 1970, 1900 (C≡O) cm^{-1}; δ_H 5.42 - 5.17 (m, 5H, ArH), 2.78 - 2.70 (m, 1H, $RCH(CH_3)N(CH_3)_2$), 2.60, 2.18 (AB part of ABX system, J_{AB} = 13.6 Hz, 2H, $ArCH_2R$), 2.27 (s, 6H, $RN(CH_3)_2$), 1.00 (d, J = 6.6 Hz, $RCH(CH_3)N(CH_3)_2$); m/z = 299(M^+); $[\alpha]_D^{20}$ - 26.5° (c, 0.1 in $CHCl_3$); (Found C, 56.1; H, 5.7; N, 4.6; $C_{14}H_{17}CrNO_3$ requires C, 56.2; H, 5.7; N, 4.7%).

General Procedure for the Preparation of (η^6-N,N-dimethyl-2-lithioamphetamine)tricarbonylchromium (0) (11)

n-Butyllithium (0.8 ml, 1.28 mmol) was added to a stirred solution of (η^6-N,N-dimethylamphetamine)tricarbonylchromium(0) (300 mg, 1.00 mmol) in THF (20 ml) at -78°C. After stirring (2 h, -78°C) the electrophile (excess) was added (vide infra):

(η^6-E-β-Methylstyrene)tricarbonylchromium(0) (12)

A solution of the anion (11) prepared as above was allowed to warm to -40°C and stirred (2 h). Methanol (1 ml) was added, the solution warmed to room temperature and evaporated. Column chromatography (Al_2O_3 Grade V, 1:4 Et_2O/petroleum ether) gave an orange gum which crystallised (CH_2Cl_2/hexane) to give the title compound as orange needles (132 mg, 52%); ν_{max} 1970, 1900 (C≡O) cm^{-1}; δ_H 6.22 and 6.16 (q, J = 6.6 Hz, 1H in total, α-proton), 6.00 and 5.95 (2s, 1H in total, β-proton), 6.00 and 5.95 (2s, 1H in total, α-proton), 5.43 - 5.20 (m, 5H, ArH), 1.88 (dd, J = 6.6 Hz, 1.5 Hz, 3H, β-methyl protons); A decoupling experiment involving irradiation of the doublet of doublets at δ1.88 gave an AB system δ6.18, 5.19 (J_{AB} = 15.7 Hz) assignable to the β- and α- protons; m/z = 254 (M^+); (Found: C, 56.4; H, 4.0; $C_{12}H_{10}CrO_3$ requires; C, 56.4; H, 4.0%).

(η^6-E-β-Methylstyrene)tricarbonyl chromium(0) (12) by complexation

A deoxygenated mixture of di-n-butyl ether (40 ml), THF (5 ml); E-β-methylstyrene (2.00 g, 16.9 mmol) and hexacarbonyl chromium (4.47 g, 20.3 mmol) was heated at reflux (24h). The cooled solution was filtered and the solvents removed. Column chromatography (Al_2O_3 grade V, 1:1 Et_2O/petroleum ether then Et_2O) gave the title compound as a yellow solid (1.05 g, 24.3%). This sample was identical in all respects to a sample of complex (12) prepared from (S)-(-)-(η^6-N,N-dimethylamphetamine)tricarbonylchromium(0) (10).

($1R$, $2S$)-(η^6-N-Methylpseudoephedrine)tricarbonylchromium(0) (15)

A solution of the anion (11) prepared as above was treated with MoOPH[12] (700 mg, 1.61 mmol). The resulting crimson solution was stirred until the reagent had dissolved (10-20 min, -78°C). Saturated aqueous Na_2SO_3 (10 ml) was added, the mixture warmed to 20°C and treated with water (40 ml). The organics were extracted with diethyl ether (3 x 40 ml) and the combined extracts concentrated and chromatographed (Al_2O_3 Grade V, Et_2O) to give a yellow solid. Crystallisation (CH_2Cl_2/hexane) gave the title compound as yellow needles (110 mg, 35%); ν_{max} 3350br (OH), 2780 ($N(CH_3)_2$), 1970, 1950, 1870br (C≡O) cm^{-1}; δ_H 5.62 (d, J = 6.7 Hz, 1H, ArH), 5.38-5.24 (m, 4H, ArH), 3.80 (d, J = 9.5 Hz, 1H, ArCHOH), 2.42 (dq, J = 9.5 Hz, 6.7 Hz, 1H, $RCH(CH_3)N(CH_3)_2$), 2.27 (s, 6H, $N(CH_3)_2$), 0.92 (d, J = 6.7 Hz, 3H, $RCH(CH_3)N(CH_3)_2$); m/z (DCI/NH_3) = 316 (M^+ + 1); $[\alpha]_D^{20}$ - 31° (c, 0.25 in $CHCl_3$); (Found: C, 53.0; H, 5.3; N, 3.9; $C_{14}H_{17}CrNO_4$ requires C, 53.3; H, 5.4; N, 4.0%).

(1S, 2R)-(η^6-2-Deuterio-N,N-dimethylamphetamine)tricarbonylchromium(0) (19).

A solution of the anion (11) prepared as above was treated with deuteriomethanol and allowed to stir (-78°C, 2 h). The solution was warmed to room temperature and concentrated. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/hexane) gave the title compound as yellow needles (285 mg, 95%); ν_{max} 2795 ($N(CH_3)_2$), 1970, 1900 (C≡O) cm^{-1}; δ_H 5.42 - 5.17 (m, 5H, ArH), 2.74 (dq, J = 6.6 Hz, 7.5 Hz, 1H, RCH(CH_3)$N(CH_3)_2$), 2.27 (s, 6H, $N(CH_3)_2$), 2.18 (d, br, J = 7.5 Hz, 1H, ArCHDR), 1.00 (d, J = 6.6 Hz, 3H, RCH(CH_3)$N(CH_3)_2$); irradiation of the doublet δ1.00 resulted in collapse of the doublet of quartets δ2.74 to a doublet δ2.74 (J = 7.5 Hz); ^2H n.m.r. (38.40 MHz, referenced to internal $CDCl_3$) 2.61; m/z = 300(M^+); $[\alpha]_D^{20}$ - 23.8° (c, 0.3 in $CHCl_3$).

(η^6-N,N-dimethylamphetamine)tricarbonylchromium(0) (10)

A solution of the anion (11) prepared as above was treated with methanol and allowed to stir (-78°C, 2 h). The solution was warmed to room temperature and concentrated. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/petroleum ether) gave a yellow solid. Crystallisation (Et_2O/hexane) gave the title compound as yellow needles (289 mg, 96%) identical in all respects with an authentic sample; $[\alpha]_D^{20}$ - 26.5° (c, 0.1 in $CHCl_3$).

(1S, 2R)-(η^6-N,N-dimethyl-2-methylamphetamine)tricarbonylchromium(0) (23).

A solution of the anion (11) prepared as above was treated with methyl iodide (0.2 ml, 3.21 mmol) and allowed to stir (-78°C, 2 h). Methanol was added, the solution warmed to room temperature and concentrated. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/petroleum ether) gave a yellow gum. Crystallisation (Et_2O/hexane) gave the title compound as orange needles (305 mg, 97%); ν_{max} 2795 ($N(CH_3)_2$), 1970, 1900 (C≡O) cm^{-1}, δ_H 5.42 - 5.21 (m, 5H, ArH), 2.57 - 2.47 (m, 1H), 2.42 - 2.32 (m, 1H), 2.23 (s, 6H, $N(CH_3)_2$), 1.32 (d, J = 6.4 Hz, 3H, ArCH(CH_3)R), 0.84 (d, J = 6.0 Hz, 3H, RCH(CH_3)$N(CH_3)_2$); m/z (DCI/NH_3) = 314 (M^+ + 1); $[\alpha]_D^{20}$- 20.2° (c, 0.45 in $CHCl_3$); (Found: C, 57.9; H, 6.4; N, 4.2; $C_{14}H_{17}CrNO_3$ requires C, 57.5; H, 6.1; N, 4.5%).

(1S, 2S)-N,N-Dimethyl-1-thiophenylamphetamine (25).

A solution of the anion (11) prepared as above was treated with a solution of phenyl-disulphide (300 mg, 1.37 mmol) in THF (3 ml) and allowed to stir (2 h, -78°C). Methanol was added and the solution was warmed to room temperature and concentrated. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/petroleum ether) gave an unstable orange oil. This was dissolved in diethyl ether (20 ml) and allowed to stand in air and sunlight until the yellow solution became colourless. Filtration (celite) gave a white solid. Crystallisation (Et_2O/hexane) gave the title compound as white needles (139 mg, 51%); ν_{max} 2790 ($N(CH_3)_2$), 1600, 1580 (Aromatic ring); δ_H 7.17 - 7.02 (m, 10H, ArH), 4.18 (d, J = 10.4 Hz, 1H, ArCHSPh), 3.12 (dq, J = 6.6 Hz, 10.4 Hz, 1H, RCH(CH_3)$N(CH_3)_2$), 2.39 (s, 6H, $N(CH_3)_2$), 0.77 (d, J = 6.6 Hz, 3H, RCH(CH_3)$N(CH_3)_2$); m/z (DCI/NH_3) = 272 (M^+ + 1); $[\alpha]_D^{20}$ + 343.7° (c, 0.6 in $CHCl_3$) ; (Found C, 75.3; H, 7.9; N, 5.0; $C_{17}H_{21}NS$ requires; C, 75.2; H. 7.8; N, 5.2%) m.p. 74°C.

(η^6-N,N-Dimethylamphetamine)tricarbonylchromium(0) (10) from (1S, 2R)(η^6-2-deuterio-N,N-dimethylamphetamine)tricarbonylchromium(0) (19)

n-Butyllithium (0.3 ml, 0.48 mmol) was added to a stirred solution of (1S, 2R)-(η^6-2-deuterio-N,N-dimethylamphetamine)tricarbonylchromium(0) (19) (100 mg, 0.33 mmol) in THF (15 ml) at -78°C. After stirring (2 h, -78°C) methanol (1 ml) was added and stirring continued (2 h, -78°C). The solution was warmed to room temperature and evaporated. Column chromatography (Al_2O_3 Grade V, 1:1 Et_2O/petroleum ether) gave a yellow solid. Crystallisation (Et_2O/hexane) gave the title compound as yellow needles (93 mg, 93%). This compound was identical in all respects with an authentic sample.

General Procedure for the Decomplexation of Complexes (15), (19) and (23).

A solution of the complex (15), (19), or (23) in diethyl ether (20 mg/ml) was allowed to stand in air and sunlight until colourless. Chromium III residues were removed by filtratrion (celite) and the ether evaporated to leave a clear oil. Where necessary further purification was achieved by flash chromatography (SiO_2, 78:20:2 toluene/EtOH/aq. NH_3) or by distillation. Yields in each case were essentially quantitative.

(1S, 2S)-N-Methylpseudophedrine (18); b.p. 77°C at 0.1 mm Hg; ν_{max} 3350br (OH), 2790 ($N(CH_3)_2$), 1600 (aromatic ring) cm^{-1}, δ_H 7.39-7.26 (m, 5H, ArH), 4.20 (d, J = 9.7, Hz, 1H, ArCHOH), 2.57 (dq, J = 9.7 Hz, 6.6 Hz, 1H, RCH(CH_3)$N(CH_3)_2$), 2.30 (s, 6H, $N(CH_3)_2$), 0.71 (d, J = 6.6 Hz, 3H, RCH(CH_3)$N(CH_3)_2$); m/z (DCI/NH_3) = 180 (M^+ + 1)' $[\alpha]_D^{20}$ + 45.9° (c, 0.44 in MeOH); Lit[16] $[\alpha]_D^{20}$ + 48.1° (MeOH)].

(1S, 2S)-2-deuterio-N,N-dimethylamphetamine (20); b.p. 58°C at 0.1 mm Hg; ν_{max} 2795 ($N(CH_3)_2$), 1600 (aromatic ring) cm^{-1}; δ_H 7.31 - 7.17 (m, 5H, ArH), 2.79 (dq, J = 9.9 Hz, 6.6 Hz, 1H, RCH(CH_3)$N(CH_3)_2$), 2.37 (d, br, J = 9.9 Hz, ArCHD), 2.34 (s, 6H, $N(CH_3)_2$), 0.93 (d, J = 6.6 Hz, 3H, RCH(CH_3)$N(CH_3)_2$); ^2H n.m.r. ($CHCl_3$, referenced to internal $CDCl_3$) 3.04; m/z = 300 (M^+).

(1S, 2S)-N,N-Dimethyl-2-methylamphetamine (24); ν_{max} 2795 ($N(CH_3)_2$), 1600 (aromatic ring) cm^{-1}; δ_H 7.31 - 7.17 (m, 5H, ArH), 2.70 - 2.59 (m, 2H, $ArCH(CH_3)CH(CH_3)N(CH_3)_2$), 2.27 (s, 6H, $N(CH_3)_2$), 1.31 (d, J = 6.5 Hz, 3H, $CH(CH_3)$), 0.64 (d, J = 6.0 Hz, $CH(CH_3)$); m/z = 177 (M^+); $[\alpha]_D^{20}$ + 15.6° (c, 0.43 in $CHCl_3$).

(1S, 2S)-N-Methylpseudophedrine (18) from (1S, 2S)-pseudoephedrine (17).

(1S, 2S)-Pseudophedrine (17)[13] (2.00 g, 12.05 mmol) was treated with formaldehyde (5 ml, 35% aqueous solution 63.11 mmol) and formic acid (1.25 ml, 98% aqueous solution, 32.47 mmol) and heated at reflux (110°, 5 h). The mixture was concentrated, treated with 2.0N NaOH (7.5 ml) and methanol (2.5 ml) and heated at reflux (100°C, 30 min). Cooling, concentration and extraction with diethyl ether gave a clear oil. Distillation (b.p. 77°C at 0.1 mmHg) gave the title compound as a low melting solid (1.34 g, 62%). This compound was identical in all respects to a sample prepared from (η^6-N,N-dimethylamphetamine)tricarbonylchromium(0) (10) (vide supra).

(1R, 2S)-(η^6-N-Methylpseudoephedrine)tricarbonylchromium(0) (15) from (1S, 2S)-N-methylpseudoephedrine (18)

A deoxygenated mixture of di-n-butyl ether (40 ml), THF (4 ml), (1S, 2S)-N-methylpseudoephedrine (18) (1.20 g, 6.70 mmol) and hexacarbonyl chromium (1.80 g, 8.18 mmol) was heated at reflux (8 h). The cooled solution was filtered and the solvents removed. Column chromatography (Al_2O_3 Grade V, Et_2O) gave the title compound as a yellow solid. Crystallisation (CH_2Cl_2/hexane) gave yellow needles (53.0 mg, 2.5%). This compound was identical in all respects to a sample prepared from (η^6-N,N-dimethylamphetamine)tricarbonylchromium(0) (10) (vide supra); $[\alpha]_D^{20}$ -30.0° (c, 0.15 in $CHCl_3$).

^{1}H n.m.r. spectral data and optical rotation for an authentic sample of (1R, 2S)-N-methylephedrine (16)[14].

δ_H 7.33 - 7.21 (m, 5H, ArH), 4.94 (d, J = 3.7 Hz, 1H, ArCH(OH)R), 2.52 (dq, J = 3.7 Hz, 6.8 Hz, 1H, $RCH(CH_3)NMe_2$), 2.34 (s, 6H, NMe_2), 0.82 (d, J = 6.8 Hz, 3H, $RCH(CH_3)NMe_2$); [Lit[14] $[\alpha]_D^{20}$ - 29.2° (MeOH)].

(1S, 2S)-(η^6-N,Methylephedrine)tricarbonylchromium (0) (14).

A deoxygenated mixture of di-n-butyl ether (75 ml) THF (7.5 ml), (1R, 2S)-N-methylephedrine (16) (2.00 g, 11.17 mmol) and hexacarbonyl chromium (3.20 g, 14.55 mmol) was heated at reflux (8 h). The cooled solution was filtered and the solvents removed. Column chromatography (Al_2O_3 Grade V, 1:2 followed by 1:1 Et_2O/petroleum ether) gave the title compound as a yellow foam (1.72 g, 49%); ν_{max} 3400br (OH), 2795 ($N(CH_3)_2$), 1980, 1970, 1880br (C≡O) cm^{-1}; δ_H 5.66 (d, J = 6.5 Hz, 1H, ArH) 5.44 - 5.24 (m, 3H, ArH), 5.17 (d, J = 6.4 Hz, 1H, ArH), 4.50 (d, J = 4.2 Hz; 1H, ArCHOH), 2.48 (dq, J = 6.7 Hz, 4 Hz, 1H, $RCH(CH_3)N(CH_3)_2$), 2.33 (s, 6H, $N(CH_3)_2$), 0.95 (d, J = 6.7 Hz, 3H, $RCH(CH_3)N(CH_3)_2$); m/z (ACE/NH_3 = 316 (M^+ + 1); $[\alpha]_D^{20}$ - 22.2° (c, 1.5 in $CHCl_3$); (Found; 53.2; H, 5.6; N, 4.2; $C_{14}H_{17}CrNO_4$ requires C, 53.3; H, 5.4; N, 4.0%).

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