The Resolution and Absolute Configuration by *X*-Ray Crystallography of the Isomeric Octopamines and Synephrines

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Racemates of the naturally occurring biogenic amines, *o*-, *m*-, and *p*-octopamine and *p*-synephrine, have been resolved by the preparation of suitable diastereoisomeric salts with antipodes of appropriate organic acids. The circular dichroism (c.d.) curves of (−)-*m*-octopamine hydrochloride and (−)-*m*-synephrine hydrochloride were superimposable and of opposite sign to those of the corresponding (−)-*p*-derivatives. *X*-Ray crystallography of the (−)-3-bromocamphor-8-sulphonate salt of (−)-*p*-synephrine confirmed (for the first time by direct means in this series of compounds) that the absolute configuration of (−)-*p*-synephrine is *R*. It is concluded from the c.d. data that the absolute configuration of (−)-*p*-octopamine is also *R*.

Octopamine, amino *p*-hydroxyphenylethanol was first identified in the posterior salivary gland of *Octopus vulgaris*.[1] This primary amine occurs in a variety of invertebrate nerve systems[2] and (together with *m*-octopamine) in small amounts in mammalian sympathetic nerves.[3,4] In mammalian tissues and body fluids, all of the isomeric octopamines occur together with the secondary amines, *m*- and *p*-synephrine [1-(4-hydroxyphenyl)-2-methylaminoethanol].[4] The octopamines and synephrines probably arise from phenylalanine *via* similar biosynthetic pathways.[5] Consequently, each of these compounds may exist naturally as a discrete enantiomer with the same absolute configuration.

In this report on isomeric octopamines and synephrines, which combines circular dichroism measurements on the separated enantiomers with the determination of the absolute configuration of (−)-*p*-synephrine by *X*-ray diffraction, we have resolved many of the ambiguities and conflicting statements found in the literature concerning the absolute configuration of these compounds.

The pharmacological effects of naturally occurring *p*-octopamine were reported to be qualitatively similar to those of synthetic racemic 2-amino *p*-hydroxyphenylethanol but quantitatively twice the activity of the racemate.[1] On this basis, and presumably by analogy with noradrenaline, the former was assumed to be the laevorotatory isomer; an assumption which may not be valid.[6] The configurations of (+)-*p*-synephrine and (−)-adrenaline were correlated with that of L(*S*)(+)-4-hydroxymandelic acid.[7] The authors concluded (using the sequence rule[8]) that natural (−)-adrenaline and (−)-*p*-synephrine have the *R* configuration.[7] The o.r.d. spectra reported for (−)- adrenaline and (−)-noradrenaline were in accordance with these assignments.[9] The configuration of (−)-*m*-synephrine was assigned as (*R*) by correlation with that of (*R*)(−)-*O*,*O*-dimethyl-*N*-acetyladrenaline;[10] this was supported by the similiarity between the o.r.d. curves of the hydrochloride salts of (−)- halostachine (2-methylamino-1-phenylethanol), (−)-*m*-synephrine and (−)-adrenaline.[11] These assignments were in agreement with the correlation[11] of (−)-halostachine with (−)-mandelic acid, which was shown recently to have the *R* configuration.[12]

The earlier conclusion[1] that natural *p*-octopamine was the (−)-isomer was propagated later by the assumption that its configuration would be the same as that of natural D(*R*)(−)-noradrenaline.[13] The o.r.d. spectrum of (+)-*p*-octopamine hydrochloride was shown as a plain positive curve while the tabulated values were those of the (−)-enantiomer.[14] Despite conflicting statements, the conclusion[14] appeared to be that (−)-*p*-octopamine had the *R* configuration by analogy with the earlier assignment of (−)-*m*-synephrine.[11] The *R* configuration was also assigned[15] to (−)-*p*-octopamine by analogy with the earlier work[7] on adrenaline but without reference to the previous conclusions concerning *p*-octopamine.[14]

In 1970 racemic *m*-octopamine was resolved and it was reported[16] that (+)-*m*-octopamine hydrochloride 'gave the same type of o.r.d. curve as D(−)-noradrenaline hydrochloride and D(−)-adrenaline hydrochloride.[9]' Consequently, Kametani *et al*[16] concluded that (+)-*m*-octopamine had the *R* configuration. In 1973 these investigations were repeated by the same workers who observed that the c.d. curve of (−)-*m*-octopamine hydrochloride was similar to that of (−)-noradrenaline hydrochloride and the configuration at C-1 of (+)-*m*-octopamine was corrected to *S*.[17]

The least ambiguous method for determining the absolute configuration of a molecule is *X*-ray diffraction. Crystal structures of numerous phenylethanolamines have been reported: noradrenaline,[18] noradrenaline hydrochloride,[19] adrenaline,[20] adrenaline hydrogen tartrate,[21] *o*-octopamine hydrochloride,[22] *m*-octopamine hydrochloride,[23] *p*-octopamine hydrochloride,[24] *m*-synephrine,[25] *m*-synephrine hydrochloride,[26] and *p*-synephrine monohydrogen phosphate.[27] Unfortunately, the structure determinations were usually carried out on the racemic form (noradrenaline, adrenaline, and *m*-synephrine are the exceptions; in which case the absolute configuration was assumed to be that derived from the chemical studies). The present investigation is the first to determine the absolute configuration of a phenylethanolamine using anomalous scattering.

Previous studies of the biological activities of isomeric octopamines and synephrines have usually used the racemates.

Table 1. Analytical data for diastereoisomers of octopamines and synephrines.

Compound (formula)	M.p./°C (lit.)	$[\alpha]_D^{22}$/° (lit., H_2O)	Found % (required) C	H	N	S	Br
(−)-2-Amino-1-(4-hydroxyphenyl)ethanol (1*S*)-(+)camphor-10-sulphonate ($C_{18}H_{27}NO_6S$)	167 (165–8d[13]) (167–168.5[15])	−6.0 (−8.0[13]) (−34[15])	56.55 (56.1)	7.4 (7.1)	3.35 (3.6)	8.0 (8.3)	
(+)2-Amino-1-(4-hydroxyphenyl)ethanol (1*S*)-(+)camphor-10-sulphonate	90 (118–141[15])	+32.0 (+138[15])	55.9	7.1	3.5	8.3	
(−)2-Amino-1-(3-hydroxyphenyl)ethanol *O,O*-dibenzoyl (+)-tartrate ($C_{26}H_{25}NO_{10}\cdot H_2O$)*	169–170	−72[a]	58.9 (59.0)	5.0 (5.1)	2.6 (2.65)		
(+)2-Amino-1-(3-hydroxyphenyl)ethanol *O,O*-dibenzoyl (−)-tartrate*	169 (160[29])	+70[a] (−67[29,b])	59.4	4.9	2.5		
(−)2-Amino-1-(2-hydroxyphenyl)ethanol *O,O*-dibenzoyl (−)-tartrate ($C_{26}H_{25}NO_{10}$)	162	−89.9[b]	60.7 (61.05)	4.6 (4.9)	2.7 (2.7)		
(+)2-Amino-1-(2-hydroxyphenyl)ethanol *O,O*-dibenzoyl (+)-tartrate	160	+84.6[b]	61.1	4.95	2.8		
(−)2-Methylamino-1-(4-hydroxyphenyl)ethanol (−)3-bromocamphor-8-sulphonate ($C_{19}H_{28}BrNO_6S$)	169–170	−84.4[a]	47.6 (47.7)	5.9 (5.9)	2.8 (2.9)	6.7 (6.7)	16.8 (16.7)
(+)2-Methylamino-1-(4-hydroxyphenyl)ethanol (+)3-bromocamphor-8-sulphonate	168–170	+85.0[a]	48.0	5.6	2.9	6.9	16.75

[a] MeOH; [b] EtOH.
* *c.f.* (−)(−)salt (m.p. 188–190,[17] 178 °C;[29] $[\alpha]_D$ +71.7,[17a] −93[29,b]): (+)(+)salt (m.p. 188–190;[17] $[\alpha]_D$ −70[17,a]).

Table 2. Analytical data for enantiomers of octopamines and synephrines.

Compound (formula)	M.p./°C (lit.)	$[\alpha]_D^{22}$/°* (lit., H_2O)	Found (%) (required) C	H	N	Cl
(**1**) (−)*p*-Octopamine HCl ($C_8H_{12}ClNO_2$)	176 (160d.[13,a,15,a])	(−)50.0 (−59.7,[28] −37.4,[13,a] −54.1,[13,a,b] −83[15,a,b])	50.3 (50.7)	6.0 (6.4)	7.1 (7.4)	18.9 (18.7)
(**2**) (+)*p*-Octopamine HCl	177 (160d.[13,a,15,a])	(+)46.0 (+58,[28] +37.2,[13,a] +56.1,[13,a,b] +86[15,a,b])	50.95	6.2	7.2	18.75
(**3**) (−)*m*-Octopamine HCl	127 (128–130[17]) (150–157[29])	(−)39.0 (−45.0,[17,c] −33[29,d])	50.3	6.35	7.2	18.7
(**4**) (+)*m*-Octopamine HCl	125 (128–130[17]) (155–160[29])	(+)37.5 (+49.8,[17,c] +39[29])	50.2	6.3	7.1	18.9
(**5**) (−)*o*-Octopamine HCl	149	(−)60.9	50.6	6.4	7.2	
(**6**) (+)*o*-Octopamine HCl	152	(+)54.7	50.5	6.35	7.3	
(**7**) (−)*p*-Synephrine HCl ($C_9H_{14}ClNO_2$)	176 (180[30,a])	(−)39.0 (−62.2[30,a,d])	52.7 (53.1)	6.5 (6.9)	6.4 (6.9)	17.8 (17.4)
(**8**) (+)*p*-Synephrine HCl	178 (180[30,a]) (179–180[7,a])	(+)42.0 (+62.2,[30,a,d] +61.5[7,a])	52.8	7.0	6.8	17.6
(**9**) (−)*m*-Synephrine HCl	141 (140–145[31])	(−)43.2 (−46.7[31,d])				
(**10**) (+)*m*-Synephrine HCl	142	(+)50.3				

* Average of five separate readings (*c* 0.1, H_2O).
[a] Free base. [b] Dilute acid. [c] MeOH. [d] Solvent unspecified.

However, when the enantiomers were used, problems arose because of the confusion between the previous notation (*d* and *l*) for the rotation and the former convention (D and L) for denoting configurations. To resolve many of the above discrepancies and ambiguities, we have separated the enantiomers of octopamines and synephrines for our pharmacological studies;[4] in this report, we characterize the enantiomers by c.d. studies and determine, for the first time, the absolute configuration of (−)-*p*-synephrine by an *X*-ray crystal structure study.

Results and Discussion

Resolution of Racemates.—Sufficient quantities of the enantiomers were resolved for chemical and pharmacological studies[4] by classical methods. Each of the pure diastereoisomers was converted into the corresponding hydrochloride salt by ion-exchange chromatography under conditions where racemisation would be minimal. The use of ion-exchange chromatography to obtain the final enantiomeric salts was most efficient and gave higher overall yields than the conventional chloride exchange in dry ether using HCl gas. The results are summarized in Tables 1 and 2. It is interesting to note that the use of (+)camphor-10-sulphonic acid to resolve racemic *p*-octopamine afforded (−)(+)- and (+)(+)-salts with physical characteristics different to those previously reported.[15] However, where comparisons were possible, good correlations were obtained with some of the published results.[13,28]

In 1956 (+)-*m*-octopamine was partially resolved by the use of *O,O*-dibenzoyl (−)-tartaric acid[29] and, using an adaptation of this method, one group[16,17] obtained (+)- and (−)-*m*-octo-

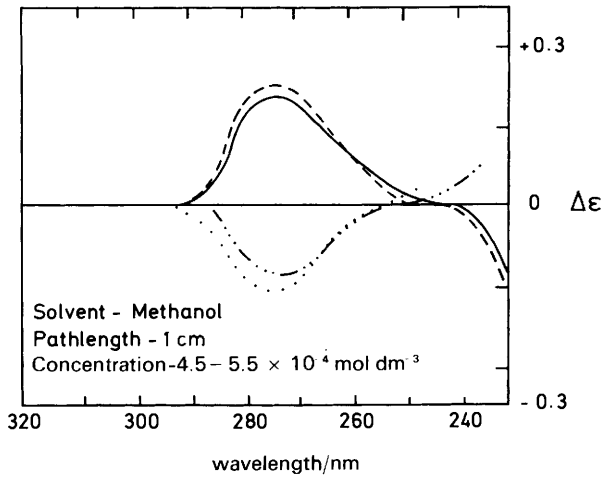

Figure 1. C.d. curves of hydrochloride salts of (−)-isomers of: *m*-synephrine (– – – –), *m*-octopamine (——), *p*-synephrine (· · · ·), *p*-octopamine (– · · · – · · · – · · · –).

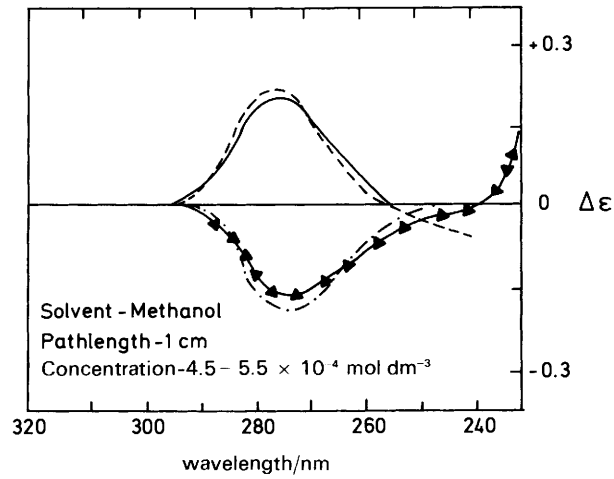

Figure 2. C.d. curves of hydrochloride salts of (+)-isomers of: *p*-synephrine (– – – –), *p*-octopamine (——), *m*-synephrine (– · – · –), *m*-octopamine (▲▲▲▲).

pamine *via* the corresponding (+)(+)- and (−)(−)-dibenzoyl tartrate salts. However, these were reported to have negative and positive rotations, respectively.[17] Repetition of this method[17] in our laboratories afforded the corresponding (−)(+)- and (+)(−)-dibenzoyl tartrates: which had similar m.p.s and optical rotations to those reported[17] for the (+)(+)- and (−)(−)-salts, respectively. However, the m.p.s and $[\alpha]_D$ values of the derived enantiomeric hydrochloride salts were in good agreement with reported values.[16,17] The enantiomeric dibenzoyl tartaric acids also proved to be suitable for the resolution of racemic *o*-octopamine.

The very brief outline published[7,30] for the resolution of (±)-*p*-synephrine has been successfully adapted and extended in this report. The physical parameters of the resultant enantiomorphs are in reasonable agreement with those published previously.[7,30] Attempts to resolve racemic *o*-synephrine using (+)-camphor-10-sulphonic acid, (+)- and (−)-bromocamphorsulphonic acid ammonium salt, and (+)- and (−)-tartaric acid were unsuccessful.

Circular Dichroism Studies.—The circular dichroism curves of the enantiomers of the hydrochloride salts of *m*- and *p*-octopamine, together with those of the corresponding

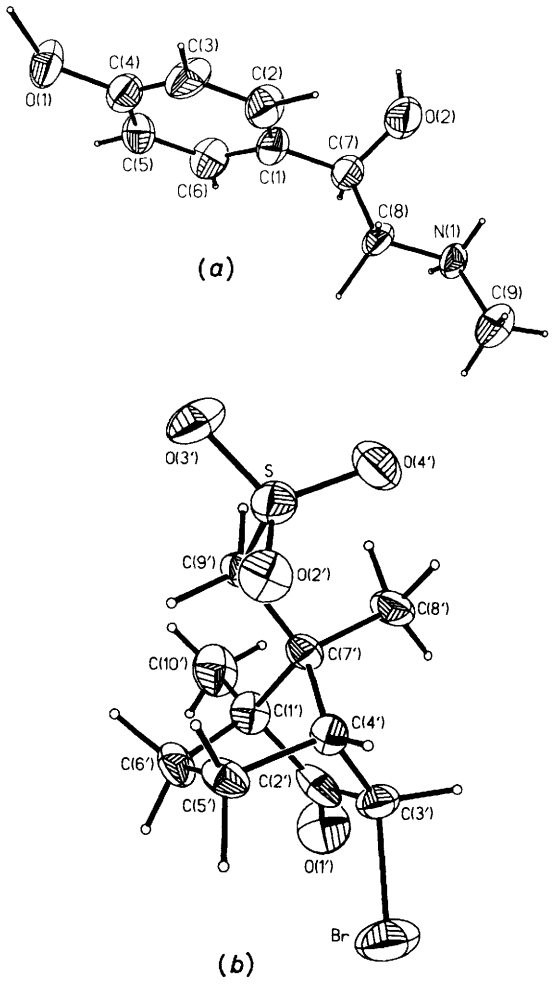

Figure 3. Molecular diagram of (*a*) the (−)-*p*-synephrine cation and (*b*) the (−)-3-bromocamphor-8-sulphonate anion showing atomic numbering and the correct absolute configuration.

synephrines, are shown in Figures 1 and 2. The enantiomers of *o*-octopamine hydrochloride did not afford a definable spectrum. The curves obtained for the (−)-*p*-isomers (Figure 1) are superimposable and, as expected, were mirror images of those of the (+)-isomers (Figure 2). A similar situation was observed for the corresponding *m*-compounds and the present results complement the curve previously obtained[17] for (−)-*m*-octopamine hydrochloride which also had a positive sign. However, the most striking feature of Figures 1 and 2 is that the sign of the curves of the *m*-enantiomers was opposite to that of the corresponding *p*-isomers. The optical rotation at 589 nm of each solution was determined both before and after the c.d. spectrum of that solution was obtained. This leads to the probable conclusion that *m*- and *p*-isomers which have the same sign of optical rotation have opposite absolute configurations and, since the absolute configuration of none of these compounds had been established unambiguously, the *X*-ray analysis of a suitable salt was undertaken.

X-*Ray Studies.*—The absolute configuration of (−)-2-methylamino-1-(4-hydroxyphenyl)ethanol (−)-3-bromocamphor-8-sulphonate was determined by an *X*-ray crystal structure study (Figure 3). The refinement of the chirality parameter, η, the *R*-value test and a comparison with the (+)-enantiomer of 3-bromocamphor-9-sulphonic acid[32–35] and 3-bromocamphor[36] are all consistent with the *R* configuration at C(1) of

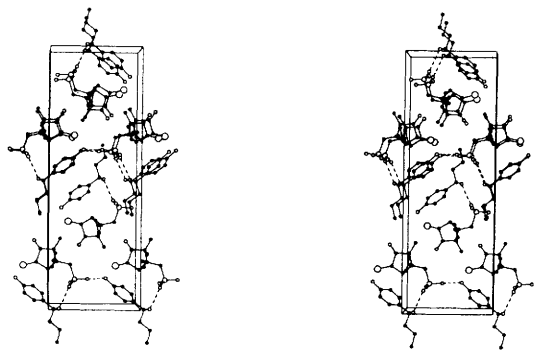

Figure 4. Stereoview of the contents of the unit cell illustrating the hydrogen bonding in the crystal.

the cation [C(7) in Figure 3(*a*)]. This confirms unequivocally the previous assignment[7] of the configuration of (−)-*p*-synephrine from chemical correlations, provides substantial support for the proposed[7] absolute configuration of (−)-adrenaline and, together with the c.d. data (Figures 1 and 2), strongly indicates that (−)-*p*-octopamine has the *R* configuration also.

The crystal structures of many biologically important asymmetric phenylethylamines have been reported:[18–27] metanephrine hydrochloride,[37] normetanephrine hydrochloride,[38] ephedrine hydrochloride,[39] ephedrine hydrogen phosphate,[40] *p*-hydroxyephedrine hydrochloride,[41] norephedrine hydrochloride,[42] *N*-methyldopamine (epinine) hydrobromide[43] and dopamine hydrochloride.[44] In spite of the large number of structural determinations on this class of compounds, the absolute configuration of none of the above was determined using anomalous scattering. The bond distances and angles in the various phenylethylamines are very similar and do not differ significantly from the values observed for the *p*-synephrine cation. The intramolecular distances from the centre of the phenyl ring to the hydroxy oxygen atom, O(2), of 3.692 Å, and to the aminonitrogen atom, N-1, of 5.121 Å are also typical of these compounds.[45]

The conformation of the cation can be described by the two torsion angles τ_1, C(6)–C(1)–C(7)–C(8) and τ_2, C(1)–C(7)–C(8)–N(1). For an extended all *trans* form τ_1 90° and τ_2 180°. In the (−)-*p*-synephrine cation the values are τ_1 69.1(5)° and τ_2 −176.5(5)°. This compares favourably with observed values in other phenylethylamines of τ_1 70–110° and τ_2 165–180°. In the monohydrogen phosphate salt of *p*-synephrine the two independent cations have τ_1 74.2° and 49.9° and τ_2 179.2° and −177.8° respectively.[27] While the extended *trans* conformation is usually observed, small variations are caused by crystal packing and hydrogen bonding. Presumably the extended *trans* form is required for biological activity which allows for maximum interaction between the β-hydroxy amino functionality and the receptor sites.

The (−)-3-bromocamphor-8-sulphonate anion has a configuration [Figure 3(*b*)] opposite to that reported for the (+)-enantiomer[32–35] and for (+)-3-bromocamphor.[36] The bond distances and angles in the anion are in agreement with the values reported for the (+)-enantiomers.[32–36] The Br atom is *endo* and the SO_3 group is *trans*-π with respect to the norbornane skeleton.

The cations and anions in the crystal are linked by four strong hydrogen bonds involving the SO_3 group oxygen atoms as acceptors as shown in the stereoview (Figure 4): the donors are the hydroxy and amino groups. The cation A in *p*-synephrine monohydrogen phosphate[27] also forms four hydrogen bonds and has a conformation almost identical with that reported here.

The *X*-ray determination of the *R* configuration of (−)-*p*-synephrine is unambiguous; it confirms the previous conclusion[7] for this compound using chemical correlations and strongly supports the previous assignment[7] (from similar evidence) of the *R* configuration for (−)-adrenaline. The superimposability of the c.d. spectra of (−)-*p*-synephrine and (−)-*p*-octopamine indicates that the latter also has the *R* configuration. It is reasonable to suppose that natural isomeric octopamines and synephrines arise *via* a common biosynthetic pathway (wherein the asymmetry at the β-carbon is created by a stereospecific enzymatic oxidation[5]) and the logical consequence would be that the asymmetric centre in each of these compounds would possess the same absolute configuration. The c.d. data of these compounds refer to optical activity associated with the lowest energy electronic transition of the phenolic chromophore and it has been claimed[46] that there is more than one spectroscopic mechanism responsible for inducing optical activity into transitions of this type. Such mechanisms will not necessarily induce the same c.d. sign and different ones may dominate in the *m*- and *p*-compounds. A less probable explanation for the observed differences in the signs of the c.d. curves may reside in different populations of rotamers about the benzyl bond. Further investigations are currently under way in our laboratories in order to resolve this apparent anomaly.

Experimental

M.p.s were determined on a Kofler micro-melting point apparatus and are uncorrected. Optical rotations were measured at room temperature in aqueous solution (unless otherwise specified) at 589 nm with a Perkin-Elmer 294 digital polarimeter and a 1 cm cell. Circular dichroism curves were determined on a JASCO J40-CS spectropolarimeter in methanol (*c ca.* 5×10^{-4} mol dm^{-3}) in a 1 cm cell from 320 to 230 nm. All the starting materials and resolving agents were obtained from Aldrich Chemical Company, Ltd. (unless otherwise stated): all ion exchange resins were obtained from BDH Chemicals Ltd. (+)- and (−)-*m*-synephrine were purchased from Ganes Chemicals, Inc., NJ, USA and Aldrich Chemical Company, Ltd., respectively. All the intermediate salts described (Table 1) were recrystallized from water or ethanol to constant m.p. and optical rotation and all final compounds (Table 2) afforded i.r., ^{1}H n.m.r., and mass spectral data consistent with their structures.

Resolution of Racemates.— (*a*)(−)-2-*Amino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (**1**). A solution of (±)-2-amino-1-(4-hydroxyphenyl)ethanol hydrochloride (20 g, 0.11 mol) in water (10 cm^3) was introduced onto a column of Dowex 50W-X8 (120 g, H^+ form) and the free base was eluted with ethanolic ammonium hydroxide (63:35, 4 mol dm^{-3}; 500 cm^3). Most of the solvent was removed by rotary evaporation at 30 °C; the precipitated base (13 g) was removed by filtration and dried *in vacuo*. (1*S*)-(+)Camphor-10-sulphonic acid monohydrate (18.5 g, 0.07 mol) was added to a solution of the free base (11.9 g, 0.07 mol) in absolute ethanol (200 cm^3). The solution was seeded with the (+)*camphor*-10-*sulphonate salt of* (−)-2-*amino*-1-(4-*hydroxyphenyl*)*ethanol* and allowed to stand at 4 °C for 12 h to obtain the (−)(+) salt (14.80 g). A solution of this colourless crystalline precipitate (4 g, 26.7%, from EtOH; 4×; Table 1) in water (10 cm^3) was applied to a column of Dowex 1-X8 (30 g, Cl^- form) which was eluted with water. The first 10 cm^3 of eluate were discarded; lyophilization of the next 25 cm^3 afforded (−)-2-*amino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (1.7 g, 86.7%, Table 2).

(*b*) (+)-2-*Amino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (**2**). The mother liquors obtained after removal of the

corresponding (−) isomer were reduced to dryness by rotary evaporation at 30 °C. A solution of the residue (15 g) in hot water (30 cm^3) was seeded with the (+)*camphor*-10-*sulphonate* salt of (+)-2-*amino*-1-(4-*hydroxyphenyl*)*ethanol* and allowed to stand at 4 °C for 12 h. The resultant (+)(+)-diastereoisomer (3.0 g, 20.0%, from H_2O; 4×; Table 1) was converted into (+)-2-*amino*-1-(4-*hydroxyphenylethanol hydrochloride* (1.0 g, 67.9%, Table 2) using Dowex 1-X8 (25 g) as before.

(*c*) (−)-2-*Amino*-1-(3-*hydroxyphenyl*)*ethanol hydrochloride* (**3**). (±)-2-Amino-1-(3-hydroxyphenyl)ethanol hydrochloride (50 g) was converted into the free base (35 g) as before, using Dowex 50W-X8 (150 g). A solution of the free base (15.8 g, 0.103 mol) in methanol (50 cm^3) was added slowly to a solution of *O,O*-dibenzoyl (+)-tartaric acid monohydrate (38.83 g, 0.103 mol) in methanol (100 cm^3), as described,[16,17] to give (−)-2-*amino*-1-(3-*hydroxyphenyl*)*ethanol* O,O-*dibenzoyl* (+)-*tartrate* (14.0 g, 53.0%, from H_2O; 4×; Table 1). This salt (4 g), dissolved in water (400 cm^3), was converted into (−)-2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride (0.9 g, 60.9%, Table 2) as described above, using Dowex 1-X8 (40 g).

(*d*) (+)-2-*Amino*-1-(3-*hydroxyphenyl*)*ethanol hydrochloride* (**4**). The racemic base (12.0 g, 0.078 mol) was reacted with *O,O*-dibenzoyl (−)-tartaric acid monohydrate (29.5 g, 0.078 mol) as before[17] to give the (+)(−) *salt* (6.0 g, 29.9%, from H_2O; 4×; Table 1). The latter (4 g) in water (400 cm^3) was applied to Dowex 1-X8 (40 g) in the manner previously described to afford (+)-2- amino-1-(3-hydroxyphenyl)ethanol hydrochloride (1.0 g, 67.6%, Table 2).

(*e*) (−)-2-*Amino*-1-(2-*hydroxyphenyl*)*ethanol hydrochloride* (**5**). A solution of (±)-2-amino-1-(2-hydroxyphenyl)ethanol (0.76 g, 0.005 mol; m.p. 97–98 °C; lit.[47] 98.5–100 °C) in absolute ethanol (10 cm^3) was added slowly to a solution of *O,O*-dibenzoyl (−)-tartaric acid monohydrate (1.88 g, 0.005 mol) in absolute ethanol (20 cm^3) and the resultant solution was heated for 5 min on a steam bath. The solvent was removed by rotary evaporation at 30 °C to give (−)-2-*amino*-1-(2-*hydroxyphenyl*)*ethanol* O,O-*dibenzoyl* (−)-*tartrate* (0.76 g, 59.8%, from H_2O; 3×; Table 1). A solution of this salt (0.3 g) in water (100 cm^3) was applied to a column of Dowex 1-X8 (3.0 g) as before to yield (−)-2-*amino*-1-(2-*hydroxyphenyl*)*ethanol hydrochloride* (0.07 g, 63.1%, Table 2).

(*f*) (+)-2-*Amino*-1-(2-*hydroxyphenyl*)*ethanol hydrochloride* (**6**). A solution of the (±) free base (1.53 g, 0.01 mol) in absolute ethanol (15 cm^3) was reacted with *O,O*-dibenzoyl (+)-tartaric acid monohydrate (3.76 g, 0.01 mol) in absolute ethanol (30 cm^3), as before, to give the corresponding (+)(+) *salt* (1.5 g, 58.7%, from H_2O; 3×; Table 1). A solution of this salt (0.5 g) in water (150 cm^3) was applied to a column of Dowex 1-X8 (5.0 g) to afford (+)-2-*amino*-1-(2-*hydroxyphenyl*)*ethanol hydrochloride* (0.11 g, 59.5%, Table 2).

(*g*) (−)-2-*Methylamino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (**7**). A solution of (−)-3-bromocamphor-8-sulphonic acid, ammonium salt (Chemical Dynamics Corp., NJ, USA; 9.85 g, 0.03 mol) in water (35 cm^3) was added slowly to a solution of the racemic free base (Sigma Chemical Co., Ltd.; 5 g, 0.03 mol) in hydrochloric acid (35.4%, 2.67 ml) and water (12.33 cm^3). The resultant solution was allowed to stand overnight at 4 °C to give (−)-2-*methylamino*-1-(4-*hydroxyphenyl*)*ethanol* (−)-3-*bromocamphorsulphonate* (4.3 g, 60.1%, from H_2O; 3×; Table 1). This salt (3.5 g), dissolved in water (50 cm^3), was converted into the corresponding (−)-*hydrochloride salt* (1.0 g, 67.3%, Table 2) using Dowex 1-X8 (30 g) in the manner previously described.

(*h*) (+)-2-*Methylamino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (**8**). This procedure was repeated with the racemic free base (10 g) and (+)-3-bromocamphor-8-sulphonic acid, ammonium salt (19. 7 g) to give the (+)(+) *salt* (10 g, 69.9%, from H_2O; 3×; Table 1), of which (4.0 g) was converted into (+)-2-*methylamino*-1-(4-*hydroxyphenyl*)*ethanol hydrochloride* (1.5 g, 88.2%, Table 2) in the usual manner with Dowex 1-X8 (30 g).

Table 3. Atomic co-ordinates (× 10^4).

	x	*y*	*z*
C(1)	4 653(8)	−556(5)	−238(2)
C(2)	3 416(8)	−1 549(6)	−278(2)
C(3)	3 746(8)	−2 600(6)	−566(2)
C(4)	5 334(8)	−2 649(6)	−814(2)
O(1)	5 705(5)	−3 624(3)	−1 117(1)
C(5)	6 605(8)	−1 657(5)	−775(2)
C(6)	6 256(9)	−639(5)	−485(2)
C(7)	4 282(9)	594(5)	69(2)
O(2)	2 549(7)	1 135(4)	8(1)
C(8)	4 359(8)	163(5)	562(2)
N(1)	3 876(7)	1 281(4)	863(1)
C(9)	3 778(10)	936(5)	1 346(2)
C(1′)	2 732(7)	586(5)	7 740(2)
C(2′)	2 940(7)	−867(6)	7 728(2)
O(1′)	3 028(6)	−1 553(4)	7 395(1)
C(3′)	2 872(7)	−1 319(5)	8 224(2)
Br	1 111(1)	−2 731(1)	8 310(1)
C(4′)	2 466(7)	−53(5)	8 479(2)
C(5′)	478(7)	379(5)	8 357(2)
C(6′)	629(7)	754(5)	7 851(2)
C(7′)	3 657(7)	909(4)	8 203(2)
C(9′)	3 423(6)	2 370(4)	8 314(2)
S	3 665(2)	2 860(1)	8 902(1)
O(2′)	2 142(4)	2 261(4)	9 155(1)
O(3′)	3 457(5)	4 268(3)	8 882(1)
O(4′)	5 447(4)	2 427(4)	9 063(1)
C(8′)	5 768(7)	577(5)	8 213(2)
C(10′)	3 423(9)	1 262(6)	7 318(2)

X-*Ray Study of the* (−)-3-*Bromocamphor*-8-*sulphonate Salt of* (−)-p-*Synephrine.*—*Crystal Data.* $C_9H_{14}NO^+{}_2{\cdot}C_{10}H_{14}BrO_4S^-$ [$C_{19}H_{28}BrNO_6S$], M = 478.41. Orthorhombic, a = 7.258(2), b = 10.309(4), c = 29.414(8) Å, U = 2 201(1) $Å^3$, (by least-squares refinement on diffractometer angles for 25 centred reflections using graphite monochromated (Mo-K_α) radiation, λ = 0.710 73 Å), space group $P2_12_12_1$, z = 4, D_c = 1.444 g cm^{-3}, $F(000)$ = 944. Crystal dimensions were 0.17 × 0.17 × 0.38 mm, μ(Mo-K_α) is 19.7 cm^{-1}.

Data collection and processing. A Nicolet R3m diffractometer and graphite monochromatized Mo-K_α radiation (λ 0.710 73 Å) were used to measure the intensity data. A θ-2θ scan technique with a variable scan speed of 2.1–29.3° min^{-1} was used to measure 3 869 reflections (h, k ±1). The intensities of two check reflections were measured after every 98 reflections. Small changes in the two standards ±2.5σ(I) were included in the data processing. A total of 2 771 reflections with $F_{obs} \geq 2\sigma F_{obs}$ were used in the analysis.

Structure solution and refinement. All calculations were carried out using the SHELXTL programs on a Data General Model 30 Desktop Eclipse.[48] The scattering factors used were taken from the usual source[49] and are included in the SHELXTL package. The position of the Br and S atoms were found by the method of a tangent refinement with random starting phases in the SHELXTL system. The remaining atoms were found in subsequent Fourier syntheses. The positional and anisotropic thermal parameters for the non-hydrogen atoms were refined by least-squares methods. A difference Fourier synthesis was used to locate 19 of the hydrogen atoms. The remaining 9 hydrogen atoms were positioned using geometrical considerations. The hydrogen atom contributions were included in the calculation with an isotropic parameter $U_{iso}{}^{12}$ = 0.06 $Å^2$ but were not refined.

Table 4. Bond lengths (Å)

(−)-Synephrine cation

C(1)–C(2)	1.367(9)	C(1)–C(6)	1.374(9)
C(1)–C(7)	1.514(8)	C(2)–C(3)	1.396(8)
C(3)–C(4)	1.365(8)	C(4)–O(1)	1.370(7)
C(4)–C(5)	1.382(8)	C(5)–C(6)	1.376(8)
C(7)–O(2)	1.388(8)	C(7)–C(8)	1.517(8)
C(8)–N(1)	1.495(7)	N(1)–C(9)	1.467(7)

(−)-3-Bromocamphor-8-sulphonate anion

C(1′)–C(2′)	1.507(8)	C(1′)–C(6′)	1.570(7)
C(1′)–C(7′)	1.552(7)	C(1′)–C(10′)	1.510(8)
C(2′)–O(1′)	1.209(7)	C(2′)–C(3′)	1.532(8)
C(3′)–Br	1.953(5)	C(3′)–C(4′)	1.534(7)
C(4′)–C(5′)	1.552(7)	C(4′)–C(7′)	1.546(7)
C(5′)–C(6′)	1.542(7)	C(7′)–C(9′)	1.550(6)
C(7′)–C(8′)	1.571(7)	C(9′)–S	1.810(5)
S–O(2′)	1.469(3)	S–O(3′)	1.461(3)
S–O(4′)	1.448(4)		

Bond angles (°)

(−)-Synephrine cation

C(2)–C(1)–C(6)	117.6(5)	C(2)–C(1)–C(7)	121.4(5)
C(6)–C(1)–C(7)	121.0(5)	C(1)–C(2)–C(3)	121.4(5)
C(2)–C(3)–C(4)	119.9(6)	C(3)–C(4)–O(1)	122.8(5)
C(3)–C(4)–C(5)	119.4(5)	O(1)–C(4)–C(5)	117.8(5)
C(4)–C(5)–C(6)	119.6(5)	C(1)–C(6)–C(5)	122.1(5)
C(1)–C(7)–O(2)	113.5(5)	C(1)–C(7)–C(8)	109.5(4)
O(2)–C(7)–C(8)	105.9(5)	C(7)–C(8)–N(1)	109.4(4)
C(8)–N(1)–C(9)	113.5(4)		

(−)-3-Bromocamphor-8-sulphonate anion

C(2′)–C(1′)–C(6′)	102.3(4)	C(2′)–C(1′)–C(7′)	101.0(4)
C(6′)–C(1′)–C(7′)	102.4(4)	C(2′)–C(1′)–C(10′)	113.9(5)
C(6′)–C(1′)–C(10′)	116.3(5)	C(7′)–C(1′)–C(10′)	118.6(4)
C(1′)–C(2′)–O(1′)	127.3(6)	C(1′)–C(2′)–C(3′)	106.0(5)
O(1′)–C(2′)–C(3′)	126.5(5)	C(2′)–C(3′)–Br	111.8(4)
C(2′)–C(3′)–C(4′)	102.3(4)	Br–C(3′)–C(4′)	116.4(3)
C(3′)–C(4′)–C(5′)	108.0(4)	C(3′)–C(4′)–C(7′)	100.5(4)
C(5′)–C(4′)–C(7′)	102.4(4)	C(4′)–C(5′)–C(6′)	103.2(4)
C(1′)–C(6′)–C(5′)	104.0(4)	C(1′)–C(7′)–C(4′)	94.6(4)
C(1′)–C(7′)–C(9′)	110.2(4)	C(4′)–C(7′)–C(9′)	116.8(4)
C(1′)–C(7′)–C(8′)	113.1(4)	C(4′)–C(7′)–C(8′)	113.3(4)
C(8′)–C(7′)–C(9′)	108.3(4)	C(7′)–C(9′)–S	117.5(3)
C(9′)–S–O(2′)	107.2(2)	C(9′)–S–O(3′)	103.2(2)
O(2′)–S–O(3′)	111.1(2)	C(8′)–S–O(4′)	108.3(2)
O(2′)–S–O(4′)	112.1(2)	O(3′)–S–O(4′)	114.3(2)

The final refinement of 253 parameters using 2 771 reflections was terminated with the maximum parameter shift of 0.02σ. The final values of R, R_w [with $w = 1/\sigma^2(F)$] and goodness of fit for the correct enantiomer (see below) were 0.061, 0.035, and 1.86, respectively. Residual peaks in the final difference map were in the range −0.71–0.65 e Å^{-3}; the highest were close to the C(3) and Br atoms.* The final positional parameters are shown in Table 3; the final bond lengths and angles for the cation and anion are given in Table 4.

Determination of Absolute Configuration.—For an assignment of absolute configuration, the chirality parameter η [50] was refined starting from η −1.0. Its final value of +1.06(3) indicates that the model used in the calculations describes the correct enantiomer. Hamilton's R-test [51] was also applied. The structure was refined using the dispersion term $\Delta f'' \pm 0$. Based on these atomic parameters, two structure-factor sets were computed: the first with $+\Delta f''$ and the second with $-\Delta f''$. Anomalous dispersion corrections for all non-H atoms were included. The R values were as follows: $R(+) = 0.0613$, $R_w(+) = 0.0354$, $R(-) = 0.0855$, and $R_w(-) = 0.0637$. The values of the theoretical ratio $R(1, 2\,518, 0.005) \simeq 1.0016$ and the experimental $R = R_w(-)/R_w(+) = 1.7994$ also confirm the choice of the configuration. The (−)-*p*-synephrine cation has the *R* configuration [Figure 3(*a*)], while the (−)-3-bromocamphor-8-sulphonate anion has the configuration 1*S*, 3*R*, 4*R*, 7*S* [Figure 3(*b*)].

* Lists of anisotropic thermal parameters, H-atom parameters, and H-bond dimensions are available on request from the Cambridge Crystallographic Data Centre. For details see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, issue 1.

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