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THE ABSOLUTE CONFIGURATION OF CRYPTOSTYLINE—III

STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CCCXCVII

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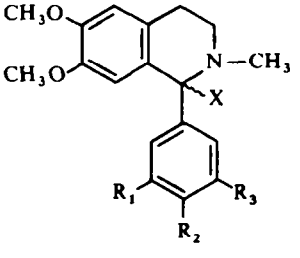
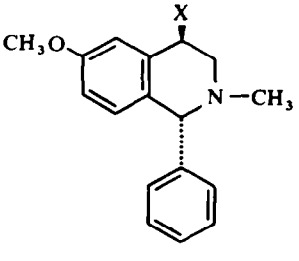
Abstract—Optical resolution of (±)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline (XII) with di-*p*-toluoyl-(+)-tartaric acid gave (−)-isoquinoline (XIII) and (+)-isomer (XIV). The former was transformed to (+)-cryptostyline III (III). A method for the stereochemical study of cryptostyline III by correlation of ORD and CD spectra with those of 1-(*R*)-phenylisoquinoline analogue (IV) is described.

CRYPTOSTYLINE I, II, III are the first 1-phenylisoquinoline alkaloids isolated from *Cryptostylis fulva Schltr.* by Leander.[2, 3] The structure of these three alkaloids was confirmed by their spectroscopic data and total syntheses,[2, 3] leaving the absolute configuration of the C-1 position unsolved. We have previously reported on the stereochemistry of (+)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-phenylisoquinoline (IV) derived from 4-hydroxyl-1-phenylisoquinoline (V).[4] We are currently investigating the determination of the absolute configuration of these 1-phenylisoquinoline alkaloids by correlation of ORD and CD spectra with those of IV as an extension of the previous work.[4] We herein wish to report these results.

SCHEME I



I: $R_1 = H$; $R_2 + R_3 = OCH_2O$; X = ◀H
II: $R_1 = H$; $R_2 = R_3 = OCH_3$; X = ◀H
III: $R_1 = R_2 = R_3 = OCH_3$; X = ◀H
VI: $R_1 = R_2 = R_3 = OCH_3$; X = ... H



IV: X = H
V: X = OH

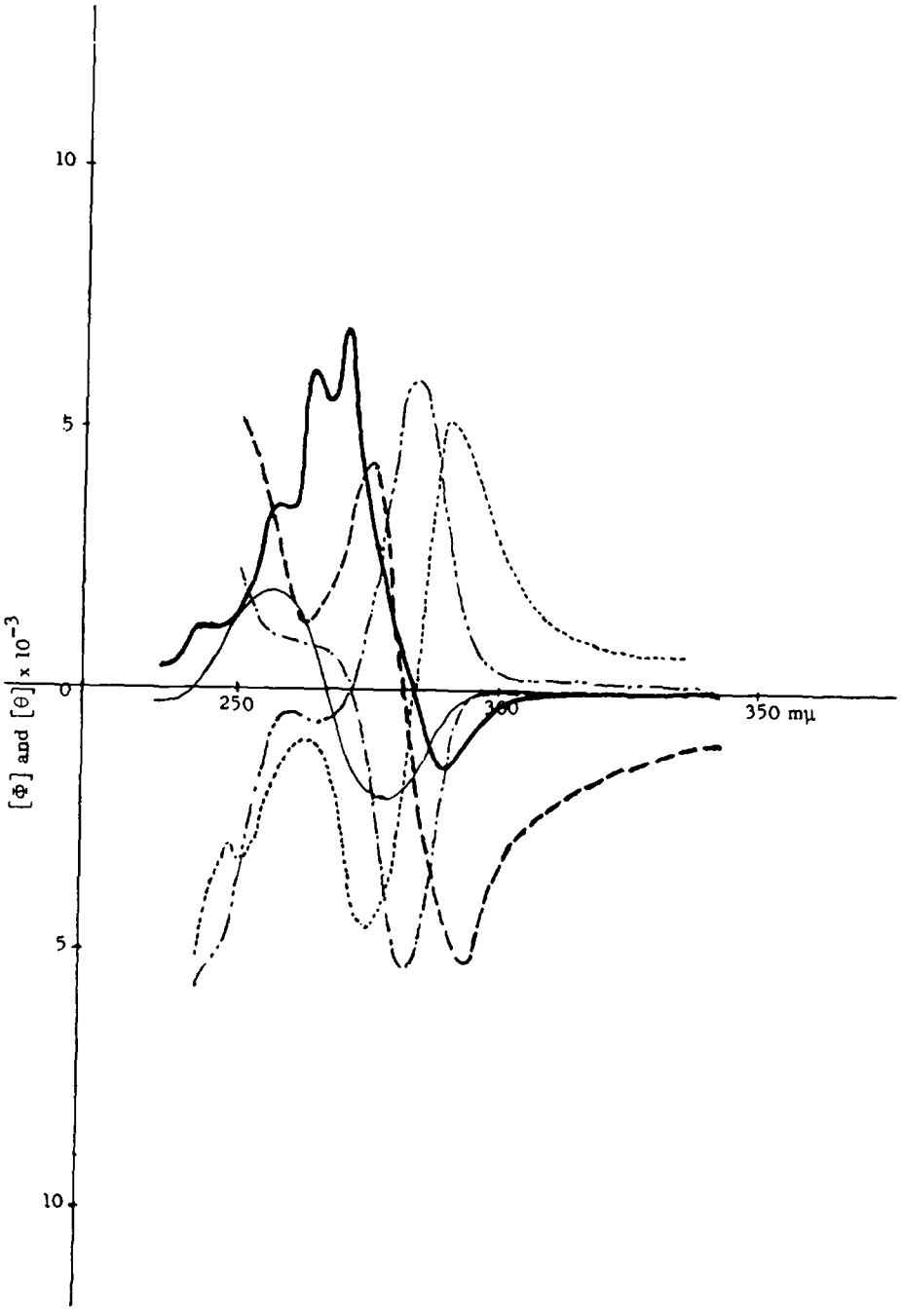


FIG 1. ORD curves of compound (IV) ———, (XIII) – – –, (XIV) - - - - - - and CD curves of compound (IV) ———, (XIII) —·—·—·—, (XIV) ———·———·——— (in MeOH)

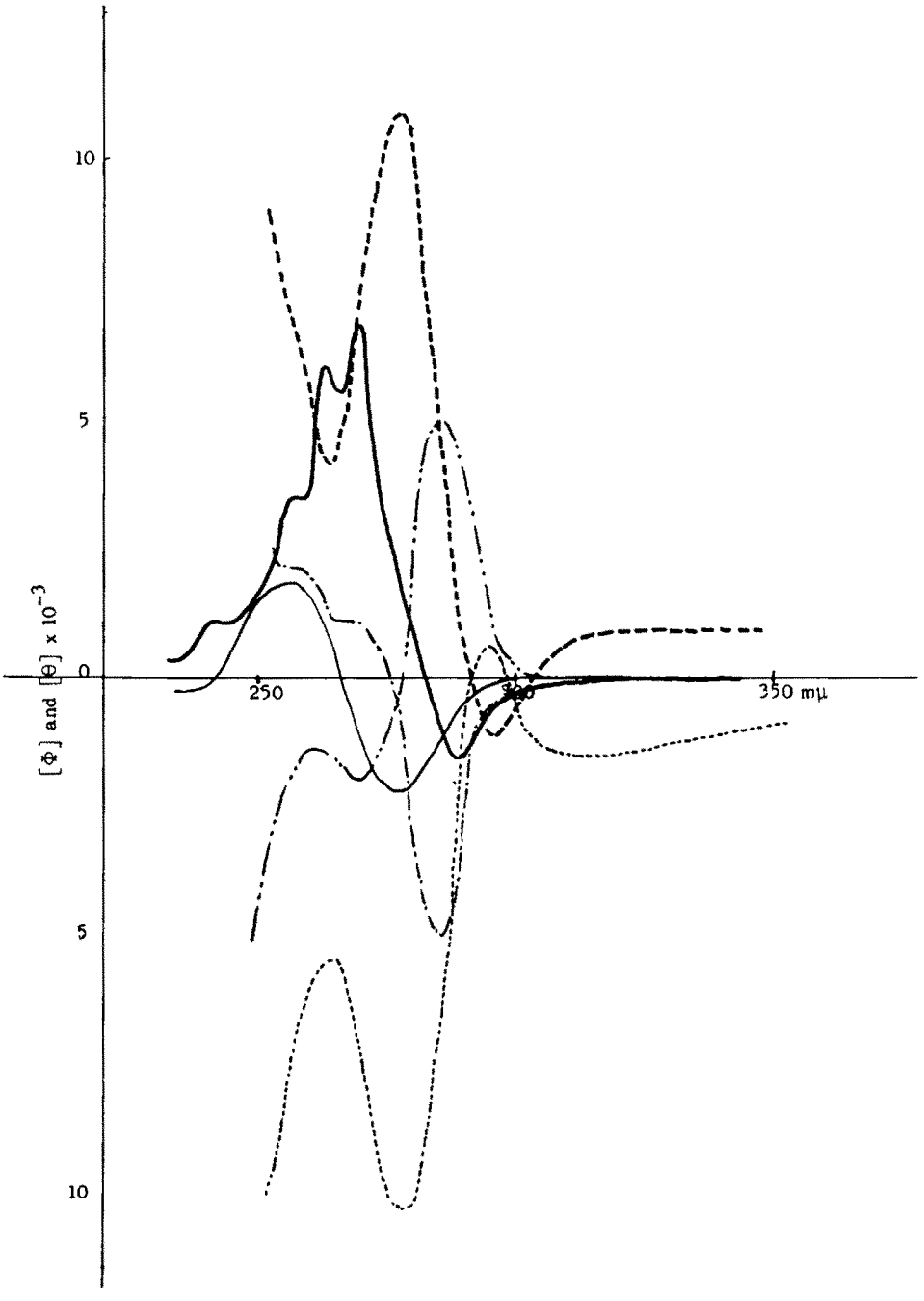
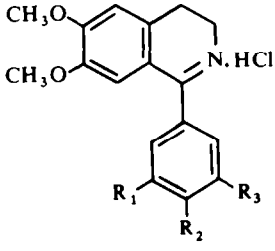


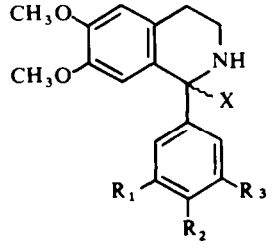
FIG 2. ORD curves of compound (III) ——, (VI) ----, (IV) ——— and CD curves of compound (III) —·—·—, (VI) —·····—, (IV) ——— (in MeOH).

First, racemic isoquinolines (X–XIII) were synthesised as follows. Reduction of 3.4-dihydroisoquinoline (VII–IX) hydrochloride. obtained by Leander's method.[2, 3] with sodium borohydride afforded the corresponding tetrahydro-isoquinolines (X, XI, and XII) as colourless needles having m.p. 135–136°, 75–76°, and 111–112°, respectively. Optical resolution of XII with di-*p*-toluoyl-(+)-tartaric acid was carried out in acetone to give (−)-XIII di-*p*-toluoyltartrate, $[[\alpha]_D^{18} -67{\cdot}1^{\circ}$ (MeOH)], which was transformed to the optically active isoquinoline (XIII) as a free base, $[[\alpha]_D^{22} -39{\cdot}9^{\circ}$ ($CHCl_3$)], as shown in Fig 1. The Eschweiler-Clarke reaction of XIII gave the optically active cryptostyline III (III), m.p. 120–121° (lit,[3] m.p. 126–129°), $[\alpha]_D^{19} +73{\cdot}8^{\circ}$ ($CHCl_3$) [lit,[3] $[\alpha]_D +51^{\circ}$ ($CHCl_3$)]. On the other hand, the optical isomer (VI) was obtained by the same manner from (+)-1,2,3,4-tetrahydro-1-(3,4,5-trimethoxyphenyl)-6,7-dimethoxyisoquinoline (XIV) which was obtained by the treatment of racemic isoquinoline (XII) with di-*p*-toluoyl-(−)-tartaric acid. The ORD spectra of these two optically active isoquinolines (III and VI) were correlated with that of the isoquinoline (IV) taking the *R*-configuration at the C-1 position. The observed results apparently indicate that the (+)-isomer (III) belongs to the *R*-series as shown in Fig 2. Therefore, the absolute configuration of the natural cryptostyline III was proved to possess a β-hydrogen at the C-1 position in the structure III.

SCHEME II



VII: $R_1 = H$; $R_2 + R_3 = OCH_2O$
VIII: $R_1 = H$; $R_2 = R_3 = OCH_3$
IX: $R_1 = R_2 = R_3 = OCH_3$



X: $R_1 = H$; $R_2 + R_3 = OCH_2O$; X = H
XI: $R_1 = H$; $R_2 = R_3 = OCH_3$; X = H
XII: $R_1 = R_2 = R_3 = OCH_3$; X = H
XIII: $R_1 = R_2 = R_3 = OCH_3$; X = ◀H
XIV: $R_1 = R_2 = R_3 = OCH_3$; X = ... H
XV: $R_1 = H$; $R_2 + R_3 = OCH_2O$; X = ◀H
XVI: $R_1 = H$; $R_2 = R_3 = OCH_3$; X = ◀H

Secondly, the optical resolution of the isoquinoline (X and XI) was examined. The treatment of X and XI with di-*p*-toluoyl-(+)-tartaric acid afforded the corresponding tartrates, $[[\alpha]_D -52{\cdot}1^{\circ}$ ($CHCl_3$)] and $[[\alpha]_D -55^{\circ}$ ($CHCl_3$)],* respectively, from which, however, the optically active isoquinolines (XV and XVI) were not obtained, but inactive ones (X and XI). These facts most certainly indicated that the isoquinolines

* These values indicated that the optical resolution of isoquinolines was carried out, since the $[\alpha]_D$ value of di-*p*-toluoyl-(+)-tartaric acid showed −86° (*c* = 1·0, MeOH) and the calculated value of the di-*p*-toluoyl-(+)-tartaric acid in the corresponding tartrate was $[\alpha]_D^{20} -101^{\circ}$ (*c* = 0·1, MeOH) in the case of di-*p*-toluoyl-(+)-tartrate of XI. This difference should be due to the optically active (−)-isoquinolines.

(XV and XVI) would be racemised in the course of liberating the corresponding di-*p*-toluoyl-(+)-tartrate by alkaline treatment. Leander[2,3] pointed out that the natural cryptostyline I (I) was easily racemised in boiling ether as in the case that some 1-phenylisoquinoline such as XV and XVI would be readily racemised with a base or in solvent. Although only (+)- and (−)- cryptostyline III were synthesised and their absolute configurations verified, it would be very difficult to obtain the other active 1-phenylisoquinolines because of ready racemisation.

EXPERIMENTAL

M.p.s are uncorrected. NMR spectra were measured by a Hitachi R-20 spectrometer. The ORD and CD spectra were taken by a JASCO model ORD/UV-5 recorder.

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4-*methylenedioxyphenyl*)*isoquinoline* (X). To a stirred soln of VII (6 g) in MeOH (100 ml) was added in small portions $NaBH_4$ (0·8 g). After the stirring for 1 hr at room temp, the solvent was evaporated and the residue was diluted with H_2O and then extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give X (6 g) as colourless needles (from Me_2CO), m.p. 135–136° (Found: C, 68·57; 5·79; N, 4·74. $C_{18}H_{19}NO_4$ requires: C, 68·99; H, 6·11; N, 4·47%); NMR (in $CDCl_3$): τ 8·09 (1H, s, NH), 6·70–7·30 (4H, m, C_3—H_2 and C_4—H_2), 6·17 and 6·35 (6H, each s, 2 × OCH_3), 5·09 (1H, s, C_1-H), 4·11 (2H, s, —O—CH_2—O), 3·76 (1H, s, C_8-H), 3·43 (1H, s, C_5-H), 3·30 (3H, s, Ar-H).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxyphenyl*)*isoquinoline* (XI). To a stirred soln of VIII (7 g) in MeOH (100 ml) was added $NaBH_4$ (0·9 g). The mixture was worked up as above to give XI (4·5 g) as colourless needles (from Et_2O), m.p. 75–76° (Found: C, 65·74; H, 7·44; N, 3·90. $C_{19}H_{25}NO_5.H_2O$ requires: C, 65·69; H, 7·25; N, 4·03%); this was further dried on P_2O_5 (3 mm Hg) at room temp to give the hemihydrate, m.p. 76–77° (Found: C, 67·51; H, 7·19; N, 4·45. $C_{19}H_{23}NO_4.0.5H_2O$ requires: C, 67·43; H, 7·15; N, 4·14%); NMR (in $CDCl_3$): τ 7·90 (1H, s, NH), 6·70–7·40 (4H. C_3—H_2 and C_4—H_2), 6·40 (3H, s, OCH_3), 5·09 (1H, s, C_1—H), 3·77 (1H, s, C_8—H), 3·42 (1H, s, C_5—H), 3·24 (3H, s, Ar—H).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*isoquinoline* (XII). A soln of IX (5 g) in MeOH (100 ml) was treated with $NaBH_4$ (1 g) and worked up as above to give XII (3·2 g) as colourless needles (from Et_2O), m.p. 111–112° (Found: C, 66·48; H, 6·80; N, 4·02. $C_{20}H_{25}NO_5$ requires: C, 66·83; H, 7·01; N, 3·90%); NMR (in $CDCl_3$): τ 7·78 (1H, s, NH), 6·75–7·40 (4H, m, C_3—H_2 and C_4—H_2), 6·39 (3H, s, OCH_3), 6·20 and 6·25 (12H, each s, 4 × OCH_3), 5·10 (1H, s, C_1—H), 3·74 (1H, s, C_8—H), 3·55 (2H, s, Ar—H), 3·43 (1H, s, C_5—H).

(−)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*isoquinoline* (XIII) *di*-p-*toluoyl*-(+)-*tartrate*. To a soln of XII (1·007 g) in Me_2CO (30 ml) was added a soln of di-*p*-toluoyl-(+)-tartaric acid (1·158 g). This mixture was kept aside for 12 hr at room temp. The ppt (1·3 g), m.p. 147–155°, was recrystallised from MeOH several times to give colourless needles (450 mg), m.p. 183–185° (Found: C, 64·09; H, 6·16; N, 2·95. $C_{20}H_{25}NO_5.0.5C_{20}H_{18}O_8.0.5H_2O$* requires: C, 64·16; H, 6·29; N, 2·50%), $[\alpha]_D^{18}$ −67·1° (*c* = 0·201, MeOH, l = 0·2 dm).

(−)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*isoquinoline* (XIII). A suspension of the above tartrate (100 mg) in 10% Na_2CO_3aq was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated. Recrystallisation of the crude product from Et_2O afforded XIII (45 mg) as colourless needles, m.p. 98° (Found: C, 66·58; H, 7·06; N, 4·15. $C_{20}H_{25}NO_5$ requires: C, 66·83; H, 7·01; N, 3·9%), $[\alpha]_D^{22}$ −39·9° (*c* = 0·326, $CHCl_3$, l = 0·2 dm), ORD (*c* 0·03), $[\Phi]_{294}$ −5300° tr, $[\Phi]_{276}$ +4300° pk, $[\Phi]_{263}$ +1250° tr; CD, $[\theta]_{305}$ 0°, $[\theta]_{283}$ −5400°, $[\theta]_{272}$ 0°.

(+)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)-2-*methylisoquinoline* (III). A mixture of XIII (100 mg), 37% HCHO (2 ml), and MeOH (20 ml) was refluxed for 0·5 hr on a water-bath. To the above soln was added $NaBH_4$ (150 mg) under cooling, and then the mixture was refluxed for 0·5 hr. After removal of the solvent, the remaining residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give III (70 mg) as colourless needles (from Et_2O), m.p. 120–121° (Found: C, 67·11; H, 6·99; N, 4·07. $C_{21}H_{27}NO_5$ requires: C, 67·54; H, 7·29; N, 3·75%), $[\alpha]_D^{19}$ +73·8° (*c* = 0·454, $CHCl_3$, l = 0·2 dm) [lit.[3] $[\alpha]_D^{19}$ +51° (*c* = 0·15, $CHCl_3$)]; ORD (*c* = 0·03), $[\Phi]_{296}$ −1140° tr, $[\Phi]_{278}$ +11000° pk, $[\Phi]_{264}$ +4120° tr; CD, $[\theta]_{286}$ −5040°, $[\theta]_{276}$ 0°.

* These salts were very hygroscopic.

(+)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*isoquinoline* (XIV) *di*-p-*Toluoyl*-(−)-*tartrate*. To a soln of XII (420 mg) in Me_2CO (13 ml) was added a solution of di-*p*-toluoyl-(−)-tartaric acid (420 mg). This mixture was worked up as above to give the tartrate (190 mg) as colourless needles (from MeOH), m.p. 183–184·5° (Found: C, 64·01; H, 6·48; N, 2·35. $C_{23}H_{25}NO_5.0.5C_{20}H_{18}O_8.0.5H_2O$* requires: C, 64·16; H, 6·29; N, 2·50%), $[\alpha]_D^{18}$ +60·7° (*c* = 0·206, MeOH, 1 = 0·2 dm).

(+)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*isoquinoline* (XIV). A suspension of the above tartrate (115 mg) in 10% Na_2CO_3 aq was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give XIV (50 mg) as colourless needles (from Et_2O), m.p. 96–97° (Found: C, 66·45; H, 6·18; N, 4·16. $C_{20}H_{25}NO_5$ requires: C, 66·83; H, 7·01; N, 3·90%). $[\alpha]_D^{18}$ +39·9° (*c* = 0·388. $CHCl_3$, 1 = 0·2 dm); ORD (*c* = 0·025), $[\Phi]_{263}$ −1000° pk, $[\Phi]_{251}$ −3300° tr, $[\Phi]_{249}$ −3000° pk; CD $[\Phi]_{284}$ +5920°, $[\theta]_{272}$ 0°, $[\theta]_{260}$ −500°.

(−)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4,5-*trimethoxyphenyl*)-2-*methylisoquinoline* (VI). The above XIV (55 mg) was treated with 37% HCHO (1·5 ml) and $NaBH_4$ (100 mg) as in the case of XIII. The crude product was recrystallised from Et_2O to give VI (30 mg) as colourless needles, m.p. 121–122° (Found: C, 67·90; H, 6·84; N, 4·05. $C_{21}H_{27}NO_5$ requires: C, 67·54; H, 7·29; N, 3·75%), $[\alpha]_D^{19}$ −82·1° (*c* = 0·176, $CHCl_3$, 1 = 0·2 dm); ORD (*c* = 0·025), $[\Phi]_{295.5}$ +600° pk, $[\Phi]_{278}$ −10400° tr, $[\Phi]_{264}$ −5400° pk; CD, $[\theta]_{302}$ 0°, $[\theta]_{286}$ +5000°, $[\theta]_{278}$ 0°, $[\theta]_{269}$ −1960°, $[\theta]_{261}$ −1340°.

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4-*methylenedioxyphenyl*)*isoquinoline di*-p-*Toluoyl*-(+)-*tartrate*. To a soln of X (939 mg) in Me_2CO (15 ml) was added a soln of di-*p*-toluoyl-(+)-tartaric acid (1·158 g) in Me_2CO. The mixture was kept aside at room temp and the ppt was recrystallised from MeOH several times to give colourless prisms (900 mg). m.p. 185–187°. (Found: C, 65·14; H, 5·98; N, 2·71. $C_{18}H_{19}NO_4 \cdot 0.5C_{20}H_{18}O_8 \cdot 0.5H_2O$[6] requires: C, 65·23; H, 5·67; N, 2·71%). $[\alpha]_D^{17}$ −52·1° (*c* = 0·240. MeOH. 1 = 0·2).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxyphenyl*)*isoquinoline di*-p-*Toluoyl*-(+)-*tartrate*. The isoquinoline XI (658 mg) was treated with di-*p*-toluoyl-(+)-tartaric acid (772 mg) in Me_2CO as above to give the tartrate (800 mg) as colourless needles, m.p. 187–189° (from MeOH) (Found: C, 65·45; H, 5·78; N, 2·95. $C_{19}H_{23}NO_4.0.5C_{20}H_{18}O_8.0.5H_2O$* requires: C, 65·59; H, 6·26; N, 2·64%), $[\alpha]_D^{19}$ −55° (*c* = 0·201, MeOH, 1 = 0·2 dm).

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