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Studies on Vasodilators. I. Synthesis and Stereochemistry of the Metabolites of Bencyclane

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Nine diastereoisomers containing a hydroxy or carbonyl group on the cycloheptane ring of bencyclane were synthesized.

Configurational analysis of γ-hydroxybencyclane was attempted in order to determine the configuration of the major bencyclane metabolite.

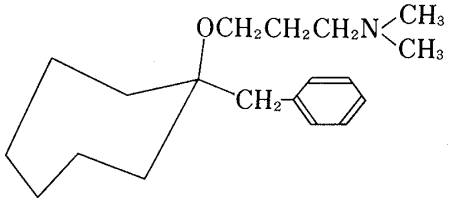
Keywords——vasodilator; antispasmodic; metabolite of bencyclane; oxygenated bencyclanes; γ-hydroxybencyclane; stereochemistry

Introduction

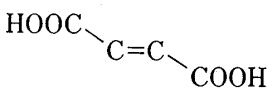
Bencyclane [I] is one of the cycloalkanoethers first synthesized by Palos *et al.*,[2)] and is now used therapeutically as a vasodilator and antispasmodic. Kimura *et al.*[3)] have recently investigated the metabolism of bencyclane in rats and men, and found new metabolites having a hydroxy group or a carbonyl group on the cycloheptane ring.

As possible structures of such oxygenated metabolites of bencyclane, nine diastereoisomers can be considered. That is, there are three positions on the cycloheptane ring at which hydroxylation could occur, and moreover two geometrical isomers (*cis* and *trans*) have to be considered for each three hydroxylated diastereoisomers.

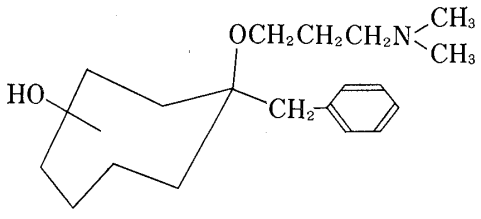
We have synthesized all such possible diastereoisomers in an effort to ensure unequivocal structural assignment, and studied their configurations by proton magnetic resonance (PMR) and carbon magnetic resonance (CMR).



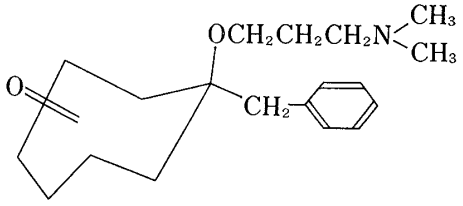
bencyclane (I)



metabolites in urine of rats and men



II, IV, VI



III, V, VII

Chart 1

1) Location: *2-1, Takatsukasa 4-chome, Takarazuka-shi, Hyogo, 665 Japan.*
2) L. Palos, G. Zolyomi, Z. Budai, E. Komlos, and L.E. Petocz, Hungarian Patent No. 151865 (1965).
3) K. Kimura, A. Nagata, and H. Miyawaki, *Xenobiotica*, 9 (12), 119 (1979).

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Results and Discussion

Synthesis of Nine Possible Diastereoisomers of Oxygenated Bencyclane

Bencyclanes containing a hydroxy or carbonyl group on the cycloheptane ring were synthesized in three ways as shown in Chart 2, 3 and 4.

Synthesis of α-Hydroxy and α-Oxobencyclane

α-Hydroxybencyclane [II] was synthesized from cycloheptanone in seven steps, as shown in Chart 2.

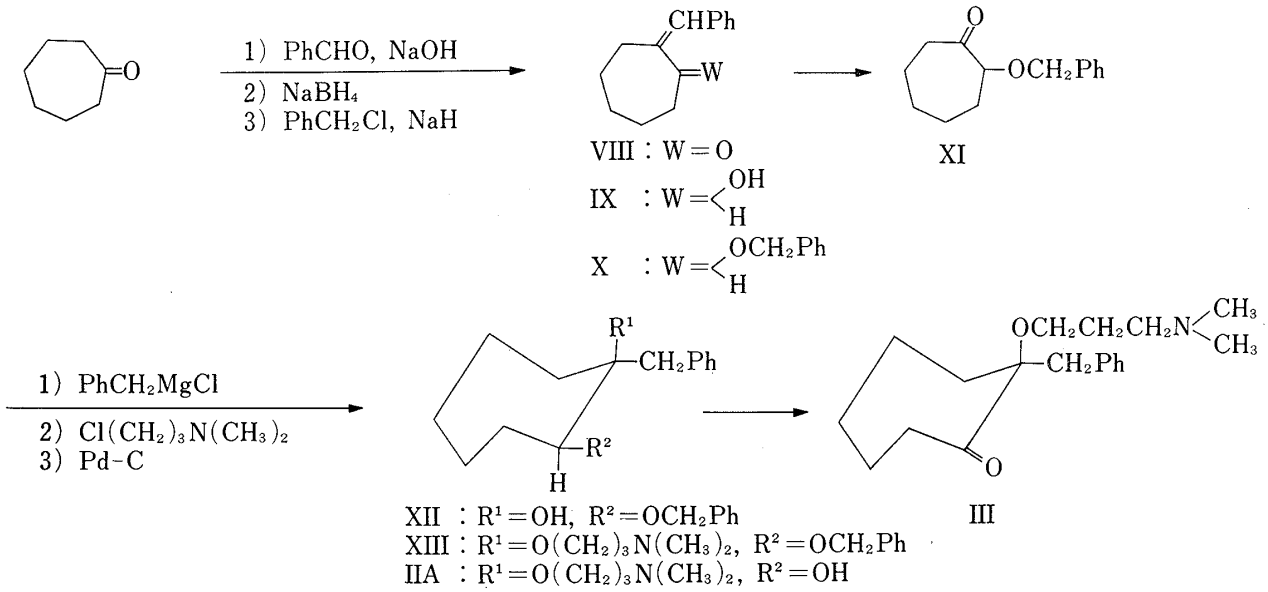

Chart 2

2-Benzylidenecycloheptanol [IX], prepared by the condensation of cycloheptanone with benzaldehyde[4] and subsequent reduction, was converted to the benzylether [X], which was then subjected to ozonization, followed by reductive cleavage with zinc powder and glacial acetic acid to give 2-benzyloxycycloheptanone [XI].

The Grignard reaction of XI with benzyl magnesium chloride gave 1-benzyl-2-benzyloxycycloheptanol [XII], which was then alkylated with an excess of 3-N,N-dimethylaminopropyl chloride in the presence of sodium hydride to give the dimethylaminopropylether [XIII]. Debenzylation of XIII proceeded in fairly good yield at room temperature to give the target α-hydroxybencyclane [IIA], and another target compound, α-oxobencyclane [III] was obtained by the oxidation of IIA with chromium trioxide (CrO_3).

The Grignard reaction of XI afforded only one product with a *cis* hydroxy group relative to the benzyloxy group, and the *trans* isomer could not be isolated. Synthesis of the *trans* isomer of IIA was achieved by the reduction of III with $NaBH_4$ as a minor product (the reaction mixture consisted of about 75% *cis* and 25% *trans*).

Synthesis of β-Hydroxy and β-Oxobencyclane

β-Hydroxybencyclane [IV] was synthesized from 2-cyclohepten-1-ol in seven steps as shown in Chart 3.

4) N. Barbulescu and A. Quilico, *Gazz. Chim. Ital.*, **91**, 326 (1961).

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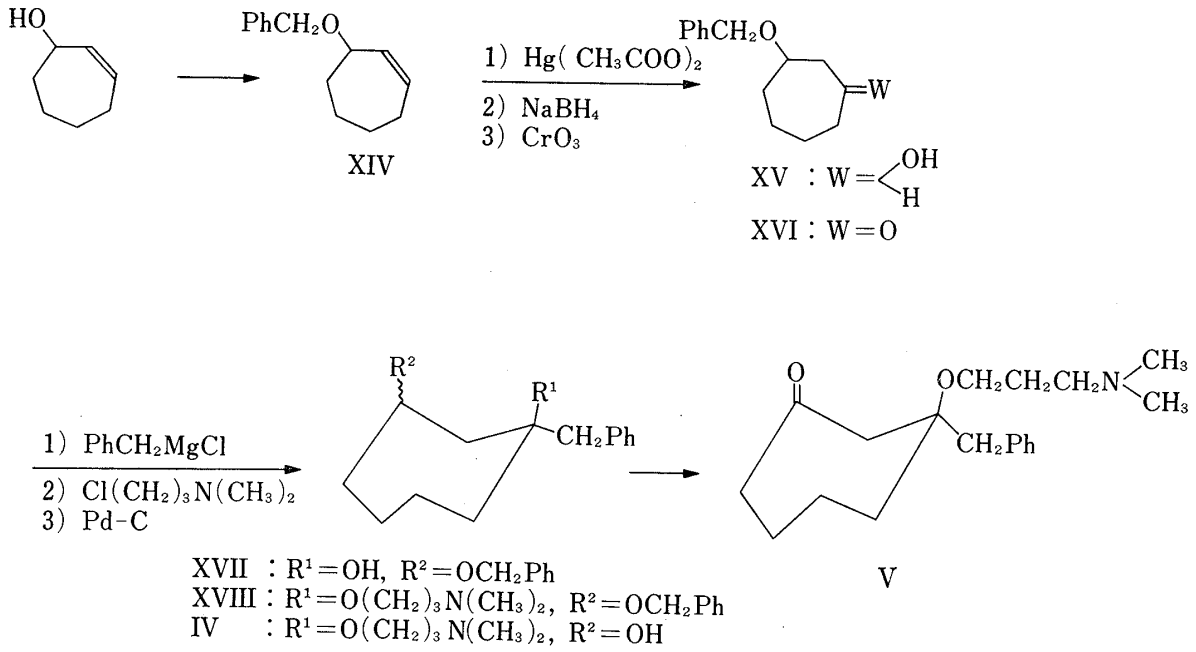

Chart 3

1-Benzyloxycyclohept-2-ene [XIV], prepared by the benzylation of 2-cyclohepten-1-ol,[5] was converted to 3-benzyloxycycloheptanol [XV] by the reaction of XIV with mercuric acetate and subsequent reduction with $NaBH_4$.

Oxidation of XV, followed by Grignard reaction with benzyl magnesium chloride afforded 1-benzyl-3-benzyloxycycloheptanol [XVII].

The alkylation of XVII, the debenzylation of XVIII and the oxidation of IV were conducted as described above to give the targets, β-hydroxybencyclane [IV] and β-oxobencyclane [V].

The Grignard reaction of XVI afforded a mixture of *cis* and *trans* 1-benzyl-3-benzyloxycycloheptanol consisting of about 20% *trans* and 80% *cis*. The details of the configurational analysis of α and β-hydroxybencyclanes will be reported in another paper.

The isomeric mixture of XVIII was separated by column chromatography on silica gel.

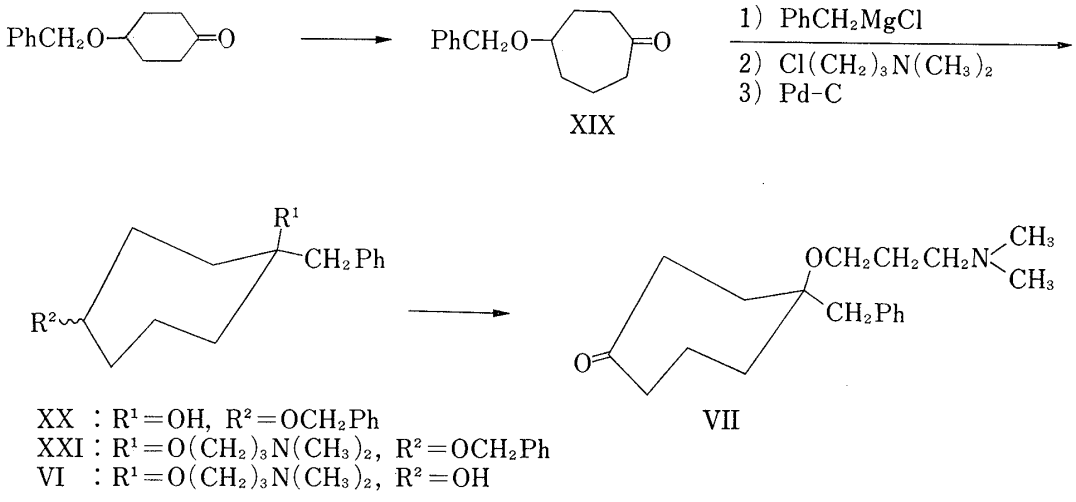

Chart 4

5) A.C. Cope, T.A. Liss, and G.W. Wood, *J. Am. Chem. Soc.*, **79**, 6287 (1957).

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Synthesis of γ-Hydroxy and γ-Oxobencyclane

γ-Hydroxybencyclane was synthesized from 4-benzyloxycyclohexanone[6] in four steps as shown in Chart 4.

Ring enlargement[7] of 4-benzyloxycyclohexanone, followed by Grignard reaction with benzyl magnesium chloride afforded a mixture of *cis* and *trans* 1-benzyl-4-benzyloxycycloheptanol [XX] consisting of about 50% *cis* and 50% *trans*, which was separated by column chromatography on silica gel.

By a procedure similar to the described above for the α and β series, the alkylation of XX, the debenzylation of XXI and the oxidation of VI were conducted in fairly good yields.

Among the hydroxy and oxobencyclanes synthesized by the procedures described above, γ-oxobencyclane and one isomer of the γ-hydroxybencyclanes were found to be identical with the major bencyclane metabolites formed in rats and men as reported by Kimura *et al.*[3]

Configurational Analysis of γ-Hydroxybencyclane

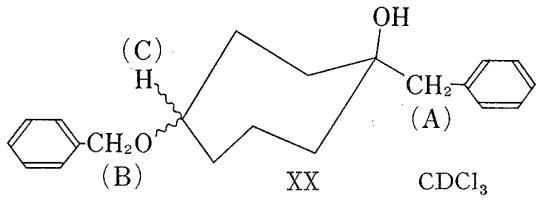
Configurational analysis of γ-hydroxybencyclane [VI] was attempted in order to determine the configuration of the metabolite by means of PMR or CMR spectroscopy and finally by synthetic approaches.

The ^1H Nuclear Magnetic Resonance (NMR) Spectrum

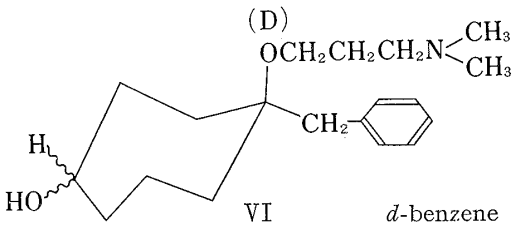
The high resolution NMR spectra of the *cis* and *trans* isomers of XX and VI were obtained at 60 Mc/s; measurements were repeated several times in order to minimize the effects of drift.

The chemical shifts in ppm to low field relative to internal tetramethylsilane for the methylene protons of the benzyl group and the benzyloxy group, the C-4 ring proton and the α-methylene protons of the 3-N,N-dimethylaminopropoxy group are listed in Table I. The compounds marked by one asterisk correspond to the metabolite and those with two asterisks are isomers.

Table I. PMR Spectra of XX and VI



XX $CDCl_3$



VI *d*-benzene

ppm	(A)	(B)	(C)	(D)
XX*	2.70	4.49	3.57	
XX**	2.72	4.49	3.57	
$\Delta\delta$ XX*−XX**	−0.02	0.00	0.00	
			ca.	
VI*	2.63		3.5	3.41
VI**	2.68		3.7	3.38
$\Delta\delta$ VI*−VI**	−0.05		−0.2	0.03

The results in Table I show that the signal of the methylene protons of the benzyl group and the signal of the C-4 ring proton in VI* lie 0.05 ppm and about 0.2 ppm to high field from the positions for the corresponding isomer [VI**], and that the signal of the α-methylene protons of the 3-N,N-dimethylaminopropoxy group lies 0.03 ppm to low field. The same

6) R.T. Gray, R.J. Spangler, and C. Djerassi, *J. Org. Chem.*, **35**, 1525 (1970).
7) P. Yates and C.D. Anderson, *Can. J. of Chem.*, **41**, 1033 (1963).

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effect is observed in *cis* and *trans* 4-methylcyclohexanol[8] and in a number of steroidal compounds.[9]

Although the present compounds have a seven-membered ring system in contrast with the above examples, we assumed that in the present systems these different shift values were also caused by a long-range effect due to the hydroxy group or the alkoxy group. That is, we considered that when the γ-hydroxy group is *cis* to the benzyl group the signal of the methylene proton of the benzyl group would be shifted to low field from its position when the two substituents are *trans*. Based on these considerations, it is suggested that the configuration of the bencyclane metabolite is *cis*, as shown in Fig. 1.

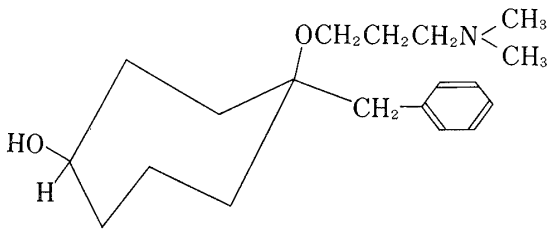

Fig. 1

The ^{13}C NMR Spectrum

The ^{13}C chemical shifts were determined of the carbons in *cis* and *trans* 1-benzyl-4-benzyloxycycloheptanol [XX].

To assign the resonance lines to specific carbons, offresonance proton decoupling was used. The results are shown in Table II; however, three resonance lines (34.540 ppm, 34.734 ppm and 40.669 ppm) could not be assigned from off-resonance results only.

Table II. CMR Spectrum of XX in $CDCl_3$

C-No.	XX*	XX**	$\Delta\delta$ XX*−XX**
1	74.382 ppm	74.616	−0.234
3	27.211	26.704	0.507
4	78.202	78.358	−0.156
6	17.971	18.439	−0.468
8	49.510	49.393	0.117
9	69.938	69.975	−0.037
2	34.540	33.136	
5	34.734	35.553	
7	40.699	41.596	

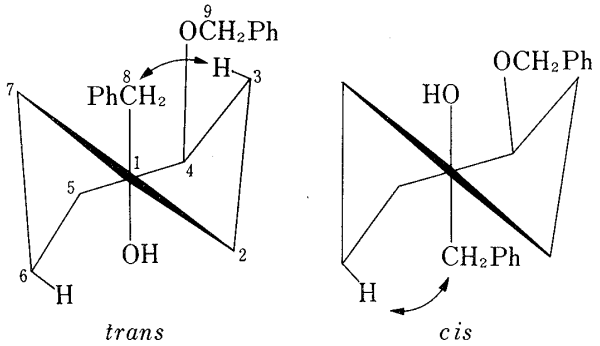

Fig. 2

We noted the two resonance lines of C-3 and C-6, because relatively large differences between *cis-trans* isomeric pairs were observed. In comparing the *cis-trans* isomeric paris, the resonance line of C-3 at 26.704 ppm in XX** is shifted upfield by 0.507 ppm, while the resonance line of C-6 at 17.971 ppm in XX* is shifted upfield by 0.468 ppm.

It is known[10] that the twist-chair conformation is the most stable in cycloheptane, and that this form has three different equatorial (e) and axial (a) positions as well as two identical isoclinal (i) or axis positions. Substituents at the i and the various e positions have been calculated to have roughly the same conformational energy.[11] Christl and Roberts[12] suggested from ^{13}C–NMR data for *cis* and *trans* 1,4-dimethylcycloheptanols that the twist-chair conformation is more stable, and that the 1-methyl group and the hydroxy group are each isoclinal and the 4-methyl is equatorial in one of the most favorable conformers.

8) J.I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).
9) N.S. Bhacca and D.H. Williams, Applications of NMR Spectroscopy in Organic Chemistry 13.
10) J.B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961); *idem*, *ibid.*, **84**, 3355 (1962).
11) J.B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7043 (1967).
12) M. Christl and J.D. Roberts, *J. Org. Chem.*, **37** (**22**), 3443 (1972).

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In the present case, we assumed on the basis of the previous reports that the twist-chair conformations shown in Fig. 2 were the most favorable.

Since the benzyl group is bulkier than the hydroxy group, it is evident from Fig. 2 that the axial hydrogen atom at C-3 of the *trans* isomer should have a larger γ-interaction than the *cis* isomer. Similarly, the γ-interaction between C-1 and C-6 should be larger in the *cis* isomer. From these considerations, we assumed that compound XX*, corresponding to the metabolite, had the *cis* configuration. This assignment is in agreement with predictions based on the ^{1}H–NMR spectra.

Stereoselective Synthesis of *cis* 1-Benzyl-1,4-cycloheptanediol

It has been established in many cases[13] that the reduction of a 1,4-peroxide bridge produces a *cis* 1,4-glycol: for example, 1,4-epidioxycyclohept-2-ene has been reduced to *cis* 1,4-cycloheptanediol.[5] Thus, we attempted to synthesize an authentic sample of *cis* 1-benzyl-1,4-cycloheptanediol by means of the synthetic sequence shown in Chart 5.

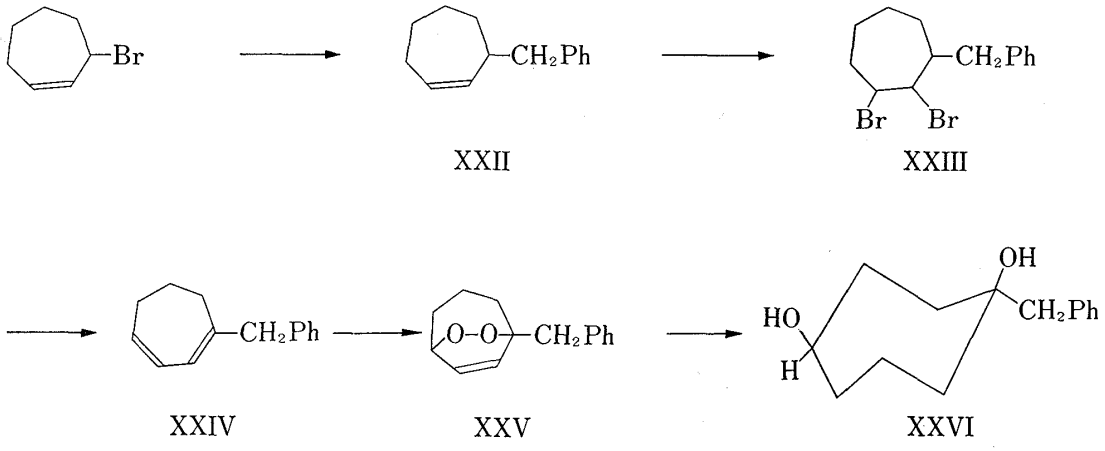

Chart 5

1-Benzylcyclohept-2-ene [XXII], obtained by the coupling reaction between 1-bromocyclohept-2-ene and benzyl magnesium chloride, was converted to the dibromide [XXIII] at low temperature, and this was treated with sodium hydroxide at 220° to give 1-benzyl-1,3-cycloheptadiene [XXIV].

The diene [XXIV] was converted to the crude peroxide, 1-benzyl-1,4-epidioxycyclohept-2-ene [XXV], by treatment with air, catalyzed by light in the presence of eosin, and then XXV was hydrogenated employing a platinum or a palladium catalyst.

The oily reaction mixture was subjected to gas-liquid chromatography (GLC) analysis under conditions such that the *cis-trans* isomeric pairs of 1-benzyl-1,4-cycloheptanediol obtained by the debenzylation of XX* and XX** could be distinguished.

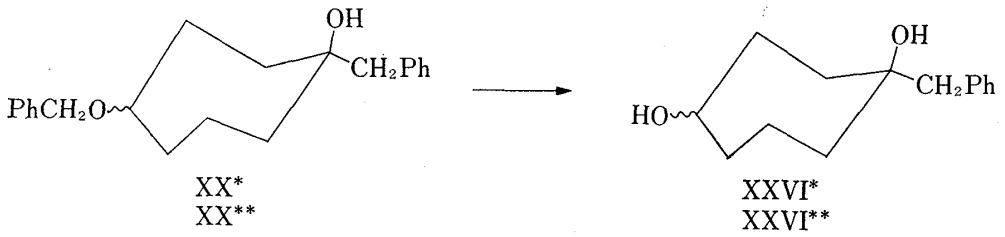

Chart 6

13) H. Paget, *J. Chem. Soc.*, **1938**, 829; G.O. Schenck, *Amgew. Chem.*, **64**, 17 (1952).

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It was found that the sole diol obtained by the hydrogenation of XXV in 8.8% yield (51% conversion from consumed starting material) had the same retention time as XXVI*, corresponding to the metabolite.

Further, this diol could be isolated by column chromatography on silica gel and was identified with XXVI* by thin-layer chromatography (TLC) and PMR.

The synthetic studies described above gave strong support to the assignment of the configuration of the metabolite as *cis*-form, as shown in Fig. 1.

Experimental

Melting points are uncorrected. The PMR spectra and CMR spectra were recorded with Varian T-60 (60 MHz) and JEOL FX-100 (25 MHz) instruments. GLC was carried out with a Hitachi 163 gas chromatograph equipped with a hydrogen flame ionization detector.

2-Benzylidenecycloheptanone [VIII]——To a mixture of cycloheptanone (29.3 g), benzaldehyde (30.4 g) and EtOH (300 ml) was added a solution of KOH (13.5 g) in water (9 ml) and EtOH (81 ml). After refluxing for 5 min, the resulting mixture was poured into water and extracted with ethyl acetate.

The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in isopropyl alcohol and after cooling, the precipitate was filtered off. The filtrate was evaporated and distilled *in vacuo* to give 17.3 g (33.1%) of VIII, bp 135—140° (1.3 mmHg), NMR (in CCl_4) δ: 6.23 (1H, s, olefinic proton).

2-Benzylidenecycloheptanol [IX]——To a solution of VIII (17.3 g) in water (18 ml) and EtOH (370 ml), $NaBH_4$ (20 g) was added in portions with stirring at room temperature.

After stirring for a further 1.5 hr, the resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4, and evaporated down, and vacuum distillation of the residual oil yielded 15 g (85.8%) of the product (IX), bp 134—141° (0.3 mmHg), NMR (in CCl_4) δ: 6.20 (1H, s, olefinic proton).

2-Benzyloxy-1-benzylidenecycloheptane [X]——To a solution fo IX (10 g) in N,N-dimethylformamide (DMF), sodium hydride (2.6 g: 69.6%) was added, then a solution of benzyl chloride (7 g) in DMF (100 ml) was immediately added dropwise.

The mixture was stirred for 6.5 hr at 70—80°, poured into water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4, evaporated down, and the residual oil was chromatographed on silica gel to afford 6.4 g (44.3%) of X, NMR (in CCl_4) δ: 4.43 (2H, AB quartet, $-OC\underline{H}_2Ph$), 6.4 (1H, s, olefinic proton).

2-Benzyloxycycloheptanone [XI]——Into a solution of X (7.7 g) in MeOH (80 ml), 3% ozone containing oxygen gas was introduced for 1 hr at room temperature. The reaction mixture was diluted with glacial acetic acid (80 ml) and ethyl acetate (100 ml), then zinc powder (100 g) was added in portions with stirring at 30—35°.

After stirring for a further 15 min at room temperature, the precipitate was filtered off, then washed with ethyl acetate and water. The combined filtrate and washing were made alkaline and extracted with ethyl acetate.

The ethyl acetate layer was washed with saturated NaCl aq., dried over Na_2SO_4, and evaporated down, and vacuum distilation of the residual oil yielded 2.8 g (48.7%) of XI, bp 114—122° (0.8 mmHg), NMR (in CCl_4) δ: 4.44 (2H, AB quartet, $-OC\underline{H}_2Ph$).

1-Benzyl-2-benzyloxycycloheptanol (XII)——Into a solution of benzyl magnesium chloride [formed from magnesium (2.1 g) and benzyl chloride (10 g)] in dry ether (50 ml), a solution of XI (10.3 g) in ether (66 ml) was added dropwise at room temperature.

After refluxing for 2 hr, the resulting mixture was poured into water containing crushed ice and then dilute hydrochloric acid was added. The separated organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated down *in vacuo* to afford 10 g (68.3%) of the crude oil (XII), NMR (in CCl_4) δ: 2.77 (2H, s, $-C\underline{H}_2Ph$), 4.45 (2H, AB quartet, $-OC\underline{H}_2Ph$).

1-Benzyl-2-benzyloxy-1-(3-N,N-dimethylaminopropoxy)cycloheptane (XIII)——To a solution of XII (8.2 g) in toluene (50 ml), sodium hydride (4 g: 69.6%) was added in portions with stirring at room temperature. After refluxing for 1.5 hr, a solution of 3-N,N-dimethylaminopropyl chloride (8.5 g) in toluene (120 ml) was added dropwise and the mixture was refluxed for 5 hr.

After cooling, the resulting mixture was poured into water, and the separated toluene layer was washed with saturated NaCl aq., dried over Na_2SO_4, and evaporated down, and the residual oil was chromatographed on silica gel to afford 2.8 g (26.8%) of XIII, NMR (in CCl_4) δ: 2.98 (2H, s, $-C\underline{H}_2Ph$), 4.47 (2H, AB quartet, $-OC\underline{H}_2Ph$).

2-Benzyl-2-(3-N,N-dimethylaminopropoxy)cycloheptanol [IIA]——A mixture of the crude XIII (2.8 g), 35% HCl aq. (8.8 ml), 10% palladium on charcoal (2 g suspended 3.5 ml of water) and EtOH (88 ml) was vigorously stirred in a hydrogen atmosphere at room temperature until the consumption of hydrogen ceased.

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The catalyst was filtered off and the filtrate was evaporated down *in vacuo*. The residue was taken up in ethyl acetate and 5% NH_3 aq.

The ethyl acetate solution was washed with water, dried over Na_2SO_4, and evaporated down, and the crude oil was chromatographed on silica gel to afford 1.2 g (55.5%) of IIa, NMR (in CCl_4) δ: 2.87 (2H, AB quartet, $-C\underline{H}_2Ph$), 3.55 (2H, t, $-OC\underline{H}_2CH_2$).

2-Benzyl-2-(3-N,N-dimethylaminopropoxy)cycloheptanone (III)——To a solution of IIA (0.51 g) in water (2.5 ml) and glacial acetic acid (10 ml), CrO_3 (1.0 g) was added in portions with stirring at room temperature. After stirring for a further 1.5 hr, the resulting mixture was poured into water, made alkaline and etracted with ethyl acetate. The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated down to afford 0.37 g (73.0%) of III, NMR (in CCl_4) δ: 3.0 (2H, AB quartet, $-C\underline{H}_2Ph$), 3.45 (2H, m, $-OC\underline{H}_2CH_2$).

Reduction of III——To a solution of III (0.1 g) in MeOH (10 ml), $NaBH_4$ (0.5 g) was added in portions at room temperature.

After stirring for a further 1.5 hr, the resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 and evaporated down to leave an oil. The composition of this crude oil was determined by GLC analysis and was as follows: *cis*=75%; *trans*=25%.

1-Benzyloxycyclohept-2-ene (XIV)——To a solution of 2-cyclohepten-1-ol (34.2 g) in DMF (400 ml), sodium hydride (21.7 g: 69%) was added in portions. After cooling, benzyl bromide (80.4 g) was added dropwise and the mixture was stirred for a further 3 hr at 130—135°. After standing overnight, the resulting mixture was poured into water, extracted with ether, washed with water, dried over Na_2SO_4, and evaporated down, and the residual oil was chromatographed on silica gel to afford 31.5 g (51.1%) of XIV, NMR (in $CDCl_3$) δ: 4.53 (2H, s, $-OC\underline{H}_2Ph$), 5.85 (2H, br, olefinic proton).

3-Benzyloxycycloheptanol [XV]——XIV (31.6 g) was added to a cooled solution of mercuric acetate (55.2 g) in water (173 ml) and THF (173 ml). After stirring for 45 min at room temperature, 12% NaOH aq. (173 ml) was added followed by a solution of $NaBH_4$ (3.4 g) in NaOH aq. (173 ml) with stirring at room temperature.

After stirring for a further 1.5 hr, mercury was filtered off and the filtrate was extracted with ether, washed with water, dried over $MgSO_4$, and evaporated down, and the residual oil was chromatographed on silica gel to afford 15.2 g (44.2%) of XV, NMR (in $CDCl_3$) δ: 4.50 (2H, s, $-OC\underline{H}_2Ph$).

3-Benzyloxycycloheptanone (XVI)——To a solution of XV (1.2 g) in glacial acetic acid (5 ml), a solution of CrO_3 (0.48 g) in water (0.3 ml) and glacial acetic acid (1.1 ml) was added dropwise at room temperature. After stirring for 0.5 hr, the resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was washed successively with saturated NaCl aq., saturated $NaHCO_3$ aq. and saturated NaCl aq., dried over Na_2SO_4 and evaporated down to afford 0.6 g (50.5%) of XVI, NMR (in CCl_4) δ: 4.42 (2H, s, $-OC\underline{H}_2Ph$).

1-Benzyl-3-benzyloxycycloheptanol (XVII)——Using a procedure similar to that described for XII, a mixture of 0.6 g of XVI, 0.1 g of magnesium and 0.7 g of benzyl chloride yielded an oil (0.8 g: 93.8%), NMR (in CCl_4) δ: 2.63 (2H, s, $-C\underline{H}_2Ph$).

1-Benzyl-3-benzyloxy-1-(3-N,N-dimethylaminopropoxy)cycloheptane (XVIII)——Using a procedure similar to that described for XIII, a mixture of 2.5 g of XVII and 3 g of 3-N,N-dimethylaminopropyl chloride yielded an oily mixture containing the *cis* and *trans* isomers of XVIII. The mixture was chromatographed on silica gel to afford two fractions: fraction 1 (0.34 g: 10.7%), NMR (in CCl_4) δ: 2.73 (2H, s, $-C\underline{H}_2Ph$), 4.36 (2H, s, $-OC\underline{H}_2Ph$) and fraction 2 (0.75 g: 23.5%), NMR (in CCl_4) δ: 2.72 (2H, AB quartet, $-C\underline{H}_2Ph$), 4.27 (2H, s, $-OC\underline{H}_2Ph$).

3-Benzyl-3-(3-N,N-dimethylaminopropoxy)cycloheptanol (IV)——Using a procedure similar to that described for IIA, 0.75 g of XVIII (fraction 2) yielded an oil (0.4 g: 69.1%), NMR (in CCl_4) δ: 2.77 (2H, s, $-C\underline{H}_2Ph$). From 0.5 g of XVIII (fraction 1), the isomer (0.3 g) was obtained, NMR (in CCl_4) δ: 2.70 (2H, s, $-C\underline{H}_2Ph$).

3-Benzyl-3-(3-N,N-dimethylaminopropoxy)cycloheptanone [V]——Using a procedure similar to that described for III, a mixture of 0.4 g of IV and 0.8 g of CrO_3 yielded an oil (0.35 g: 88%), NMR (in CCl_4) δ: 2.80 (2H, s, $-C\underline{H}_2Ph$).

4-Benzyloxycycloheptanone (XIX)——Utilizing a modification of a previously described procedure,[7] XIX was obtained in 39% yield, bp 122—134° (0.2 mmHg).

1-Benzyl-4-benzyloxycycloheptanol (XX)——Using a procedure similar to that described for XII, a mixture of 9.6 g of XIX and 11.7 g of benzyl chloride yielded a crude oil (10 g: 73.2%).

The isomeric mixture was separated by column chromatography on silica gel.

1-Benzyl-4-benzyloxy-1-(3-N,N-dimethylaminopropoxy)cycloheptane (XXI)——Using a procedure similar to that described for XIII, a mixture of 15.6 g of XX and 16.1 g of 3-N,N-dimethylaminopropyl chloride yielded a crude oil (21 g), NMR (in CCl_4) δ: 2.74 (2H, s, $-C\underline{H}_2Ph$).

4-Benzyl-4-(3-N,N-dimethylaminopropoxy)cycloheptanol [VI]——Using a procedure similar to that described for IIA, 163.3 g of XXI yielded a crude oil (107 g: 84.9%).

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The crude oil was chromatographed on silica gel to afford two fractions. Fraction 1 was the *trans* (33.5 g) and fraction 2 was the *cis* (27.7 g) isomer. The fumarate of the *cis* isomer crystallized from acetone as colorless crystals, mp 100—104°. *Anal.* Calcd. for $C_{23}H_{35}NO_6$: C, 65.53; H, 8.37; N, 3.32. Found: C, 65.1; H, 8.2; N, 3.4.

4-Benzyl-4-(3-N,N-dimethylaminopropoxy)cycloheptanone (VII)——Using a procedure similar to that described for III, 0.85 g of VI yielded an oil (0.6 g: 71.1%), NMR (in CCl_4) δ: 2.75 (2H, s, $-C\underline{H}_2Ph$). The fumarate of VII crystallized from isopropyl alcohol as pale yellow crystals, mp 144—145°. *Anal.* Calcd. for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.6; H, 7.9; N, 3.0.

1-Benzylcyclohept-2-ene [XXII]——To a solution of 1-bromocyclohept-2-ene (71.4 g) in dry ether (410 ml), a solution of benzyl magnesium chloride [formed from magnesium (10.0 g) and benzyl chloride (52.3 g)] in dry ether (320 ml) was added dropwise with stirring at room temperature. After stirring for 2 hr at room temperature, the resulting mixture was poured into water containing crushed ice and then dilute hydrochloric acid was added. The separated organic layer was washed with saturated NaCl aq., dried over Na_2SO_4, and evaporated down, and vacuum distillation of the residual oil yielded 65 g (85.6%) of XXII, 70—110° (0.4 mmHg).

1-Benzyl-1,3-cycloheptadiene [XXIV]——Br_2 (57.2 g) in CCl_4 (100 ml) was added dropwise to a solution of XXII (65 g) in CCl_4 (220 ml) at -10—0° and the mixture was evaporated *in vacuo* to leave an oil (XXIII), which was added to a solution of NaOH (65 g) in ethylene glycol (130 ml) at 230°. After stirring for a further 15 min at 220—240°, the resulting mixture was poured into water containing crushed ice and extracted with toluene. The toluene layer was washed with saturated NaCl aq., dried over Na_2SO_4, and evaporated, and vacuum distillation of the residual oil yielded 19.2 g (29.9%) of XXIV, bp 87—97° (0.25 mmHg), NMR (in CCl_4) δ: 3.32 (2H, s, $-C\underline{H}_2Ph$).

***cis*-1-Benzyl-1,4-cycloheptanediol [XXVI]**——A mixture of XXIV (3.0 g), the sodium salt of eosin (0.3 g) and dry MeOH (180 ml) was irradiated in a glass flask with a high-pressure mercury lamp (300 watts) at 20° for a period of 14.5 hr.

The organic layer was washed with saturated NaCl aq., and dried over Na_2SO_4. After filtration, the filtrate was diluted with EtOH (150 ml) and 10% palladium on charcoal (1 g suspended in 1 g of water) was added. The mixture was stirred vigorously in a hydrogen atmosphere at room temperature until the consumption of hydrogen ceased. The catalyst was filtered off and the filtrate was evaporated down *in vacuo* to leave an oil (3.1 g).

The composition of this crude oil was determined by GLC analysis and was as follows: benzylcycloheptane (72.1%); dibenzyl (10.6%); *cis* diol (8.8%); unknown oil (4.8%).

GLC analysis——A glass column (200 × 0.3 cm) was filled with 2% OV-225. The column temperature was 230° while the injector and detector temperatures were maintained at 300°.

Nitrogen was used as a carrier gas at a flow rate of 35 ml/min.

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