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The Nuclear Magnetic Resonance Spectra and Optical Rotatory Dispersion of Berbamunine, Magnoline and Two Diastereoisomers[1]

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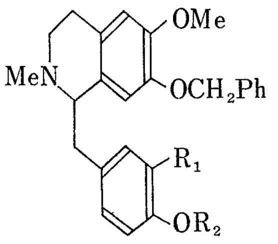
The NMR spectra and ORD curves of berbamunine, magnoline and two corresponding diastereoisomers and O,O,O-tribenzyl derivatives were investigated, in the latter of which an interesting change was observed on being set aside at room temperature for a long time.

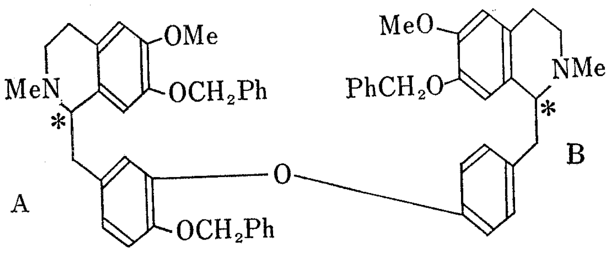
In the previous papers[3,4] we have reported the optical resolutions of (±)-7,4′-O,O-dibenzyl-3′-bromo-N-methylcoclaurine (I) and (±)-7-benzyl-N-methylcoclaurine (II) and the total syntheses of berbamunine (IX), O-methyldauricine and magnoline (X) by Ullmann reaction of the above optically active isoquinolines.

The purpose of the present investigation was to study the synthesis of the last active compound (VII) among four biscoclaurine-type compounds in order to examine the NMR



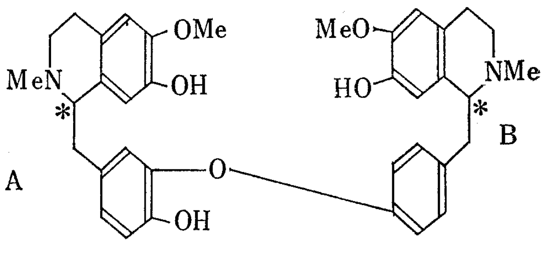
L(+)-I : R_1=Br, R_2=CH_2Ph

L(+)-Ⅱ : R_1=R_2=H



absolute configuration

	A	B
Ⅲ :	(*S*)(+)	(*S*)(+)
Ⅳ :	(*R*)(−)	(*R*)(−)
Ⅴ :	(*R*)(−)	(*S*)(+)
Ⅵ :	(*S*)(+)	(*R*)(−)
Ⅺ :	(*R*)(−)	(±)



absolute configuration

	A	B
Ⅶ :	(*S*)(+)	(*S*)(+)
Ⅷ :	(*R*)(−)	(*R*)(−)
Ⅸ :	(*R*)(−)	(*S*)(+)
Ⅹ :	(*S*)(+)	(*R*)(−)
Ⅻ :	(*R*)(−)	(±)

Chart 1

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[1] This forms Part CCCXXXIV of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.

[2] Location: *a*) *Aobayama, Sendai*; *b*) *Kashiwagi, Shinjuku, Tokyo.*

[3] T. Kametani, K. Sakurai, and H. Iida, *Yakugaku Zasshi*, **88**, 1163 (1968).

[4] T. Kametani, H. Iida, and K. Sakurai, *J. Chem. Soc.* (*C*), **1969**, 500.

spectra and ORD curves of berbamunine,⁵⁾ magnoline⁵⁾ and two diastereoisomers, leading eventually to an interesting result in case of the corresponding O,O,O-tribenzyl derivatives from the NMR spectral point of view.

Ullmann reaction between (*S*)(+)-I and (*S*)(+)-II gave O,O,O-tribenzyl derivative (III), which was characterised as its dipicrate. Hydrolysis of III with ethanolic concentrated hydrochloric acid afforded the compound (VII) as a colorless powder, whose NMR spectrum was superimposable on that of VIII. From the spectral and optical points of view, this compound (VII) was found to be an antipode of VIII and related to the diastereoisomer against berbamunine (IX) and magnoline (X).

Table I. The Optical Rotation of Four Optically Active Berbamunine Type Compounds and Its O,O,O-Tribenzyl Derivatives

	O,O,O-Tribenzyl derivative		Debenzylated compound	
(+)(+)Free base	III	$[\alpha]_D^{18}$ +37.6° ($CHCl_3$)	VII	$[\alpha]_D^{18}$ +131.7° (MeOH)
dipicrate		$[\alpha]_D^{18}$ +70.1° ($CHCl_3$)		
(−)(−)Free base	IV	$[\alpha]_D^{18}$ −36.6° ($CHCl_3$)	VIII	$[\alpha]_D^{14}$ −137.9° (MeOH)
dipicrate		$[\alpha]_D^{16}$ −65.7° ($CHCl_3$)		
(−)(+)Free base	V	$[\alpha]_D^{9}$ +27° ($CHCl_3$)	IX	$[\alpha]_D^{9}$ +90.9° (MeOH);
dipicrate		$[\alpha]_D^{9}$ +20° ($CHCl_3$)		$[\alpha]_D^{9}$ +53.3° (Me_2CO)
(+)(−)Free base	IV	$[\alpha]_D^{15}$ −30.0° ($CHCl_3$)	X	$[\alpha]_D^{24}$ −85.8° (MeOH);
dipicrate		$[\alpha]_D^{22}$ −23.7° ($CHCl_3$)		$[\alpha]_D^{28}$ −9.9° (pyridine)

Table II. The 100 Mc NMR Spectra (τ in $CDCl_3$) of Berbamunine, Magnoline and Two Diastereoisomers

	N-$C\underline{H}_3$	O-$C\underline{H}_3$	C_8-H	Aromatic protons
VII	7.57 (3H) 7.52 (3H)	6.19 (6H)	3.76 (1H) 3.71 (1H)	3.53—2.95 (9H)
VIII	7.57 (3H) 7.51 (3H)	6.16 (6H)	3.74 (1H) 3.70 (1H)	3.51—2.91 (9H)
Berbamunine IX	7.56 (3H) 7.51 (3H)	6.18 (6H) 6.16 (3H)	3.78 (1H) 3.67 (1H)	3.52—3.01 (9H)
Magnoline X	7.58 (3H) 7.50 (3H)	6.19 (3H) 6.18 (3H)	3.79 (1H) 3.71 (1H)	3.54—2.92 (9H)

On comparison of the NMR spectra of O,O,O-tribenzyl derivatives, O,O,O-tribenzylberbamunine (V) and O,O,O-tribenzylmagnoline (VI) showed the methoxyl protons as singlet at nearly τ 6.16—6.18, whereas the compounds (III) and (IV) revealed two singlets due to methoxyl groups at nearly τ 6.20 and 6.18. On the other hand, regarding the debenzylated compounds the signals of the methoxyl protons were observed as two singlets at nearly τ 6.18 and 6.19 in case of IX and X, and those of VII and VIII were shown as singlet at nearly τ 6.16—6.19. Namely, there appeared a difference in the chemical shift of methoxyl groups because of the dissimilarity of absolute configuration. Furthermore, it is of interest that the C_8-proton of tribenzyl derivatives appeared as two singlets at nearly τ 3.75—3.80 and 3.78—3.82 but, on being set aside at room temperature for more than 20 days, the above two singlets became a singlet at nearly τ 3.85—3.89. In this case the IR spectra (in $CHCl_3$) of both samples as above were identical each other.

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5) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa Publishing Co., Inc., Tokyo and Elsevier Publishing Company, Amsterdam, 1968, p. 236.

The IR spectra (in KBr) of VII and VIII were identical, but there appeared a difference between the compound (VII) and berbamunine (IX) [or magnoline (X)] in the field at 900—750 cm^{-1}.

Table III. The 100 Mc NMR Spectra (τ in $CDCl_3$) of O,O,O-Tribenzyl Derivatives

	N-C$\underline{H}_3$	O-C$\underline{H}_3$	OC$\underline{H}_2$Ph	C_8-H	Aromatic
III	7.55 (3H) 7.52 (3H)	6.20 (3H) 6.19 (3H)	5.16 (4H) 5.01 (2H)	3.82 (1H) 3.80 (1H)	3.46—2.75 (24H)
*	7.53 (3H) 7.49 (3H)	6.20 (3H) 6.18 (3H)	5.18 (4H) 4.98 (2H)	3.85 (2H)	3.47—2.73 (24H)
IV	7.55 (3H) 7.51 (3H)	6.17 (3H) 6.15 (3H)	5.11 (4H) 4.98 (2H)	3.79 (1H) 3.75 (1H)	3.44—2.62 (24H)
*	7.52 (3H) 7.49 (3H)	6.20 (3H) 6.18 (3H)	5.18 (4H) 4.98 (2H)	3.85 (2H)	3.47—2.72 (24H)
O,O,O-Tribenzylberbamunine (V)	7.55 (3H) 7.51 (3H)	6.16 (6H)	5.11 (4H) 4.98 (2H)	3.78 (1H) 3.75 (1H)	3.44—2.67 (24H)
*	7.48 (3H) 7.41 (3H)	6.17 (6H)	5.18 (4H) 5.00 (2H)	3.89 (2H)	3.45—2.75 (24H)
O,O,O-Tribenzylmagnoline (VI)*	7.50 (3H) 7.43 (3H)	6.18 (6H)	5.20 (4H) 5.02 (2H)	3.88 (2H)	3.45—2.68 (24H)
XI	7.57 (3H) 7.52 (3H)	6.20 (6H)	5.18 (4H) 5.02 (2H)	3.84 (1H) 3.82 (1H)	3.47—2.71 (24H)
*	7.54 (3H) 7.49 (3H)	6.19 (6H)	5.18 (4H) 5.02 (2H)	3.85 (2H)	3.47—2.72 (24H)

* The spectra were taken after the substance had been set aside at room temperature for more than 20 days.

On the other hand, the 1-benzyltetrahydroisoquinolines show three Cotton effects in the region 300—200 mμ[6—9]; the first Cotton effect at about 280 mμ, the second Cotton effect at about 240 mμ and the third Cotton effect at about 210 mμ are observed generally. The absolute configuration of these compounds are known,[10] and all the (*S*)(L)-series have three positive Cotton effects, while the enantiomeric (*R*)(D)-compounds have three negative Cotton effects.

Battersby and his co-workers[6] had studied the optical rotatory dispersion for an extensive series of bisbenzyltetrahydroisoquinoline alkaloids containing two biphenyl ether linkages and related the curves to the stereochemistry. In the present work CD and ORD curves of our synthetic samples with monobiphenyl ether linkage were measured. The ORD and CD data for berbamunine (IX), magnoline (X), a pair of its epimers (VII and VIII) and a pair of O,O,O-tribenzyl derivatives of the latter compounds (III and IV) are summarised in Table IV and V, respectively, and the representative curves are shown in Fig. 1—3.

It would be expected that the rotation of bisbenzyltetrahydroisoquinolines containing only one biphenyl ether linkage follows an additive rule more than that of the compounds with two biphenyl ether linkages. However, on the basis of both ORD and CD data, compounds with two dissimilar centres, namely berbamunine and magnoline, have a relatively simple curve with two Cotton effects of the same sign in the region 300—230 mμ (*e.g.*, Fig. 1), while

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6) A.R. Battersby, I.R.C. Bick, W. Klyne, J.P. Jennings, P.M. Scopes, and M.J. Vernengo, *J. Chem. Soc.*, **1965**, 2239.

7) S.M. Albonico, J. Comin, A.M. Kuck, E. Sanchez, P.M. Scopes, R.J. Swan, and M.J. Vernengo, *J. Chem. Soc.* (*C*), **1966**, 1340.

8) J.C. Craig and S.K. Roy, *Tetrahedron*, **21**, 401 (1965); J.C. Craig, M. Martin-Smith, S.K. Roy, and J.B. Stenlake, *ibid.*, **22**, 1335 (1966).

9) T. Kametani and M. Ihara, *J. Chem. Soc.* (*C*), **1968**, 1305.

10) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 899 (1965).

compounds with two similar asymmetric centres (either both (R) or both (S)) have the other minor extrema between the first Cotton effect and the second Cotton effect (*e.g.*, Fig. 2 and 3).

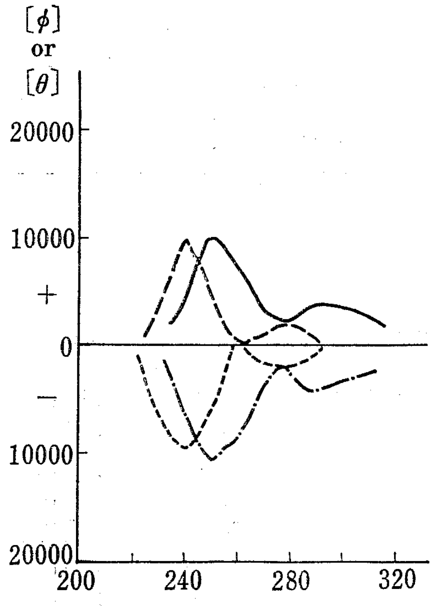


Fig. 1

ORD curve (——) and CD curve (– – –) of berbamunine (IX) and ORD curve (–•–•–) and CD curve (------) of magnoline (X)

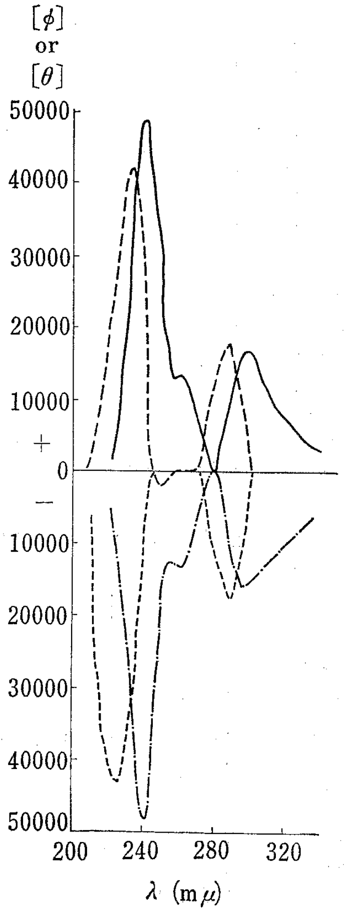


Fig. 2

ORD curve (——) and CD curve (– – –) of VII and ORD curve (–•–•–) and CD curve (------) of VIII

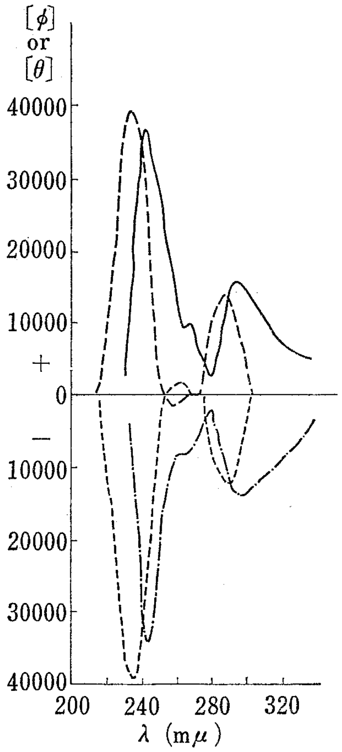


Fig. 3

ORD curve (——) and CD curve (– – –) of III and ORD curve (–•–•–) and CD curve (------) of IV

This is not as would be expected if the contributions of the molecule as a whole are additive. In this case, therefore, it appears that the over–all molecular shape (which is determined not only by the configurations of the asymmetric centres but also by the conformations of the ether bridge) is a major factor in determining the form of the curves. However, the molecular rotations seem to follow considerably the additive rule.

It is interesting that in both ORD and CD curves the second Cotton effect of the (S R)-bases occurs clearly at a longer wave length than that of the compounds with two similar asymmetric centres. Our present theoretical knowledge permits us to offer only empirical correlation between the Cotton effect and configuration for compounds of the known structure, but these may help in allotting configurations to newly discovered compounds.

On the other hand, the Ullmann reaction of (R)(−)-I with (±)-II was carried out, in order to investigate whether the separation of two diasteroisomers, (IV) and (V), would be possible or not and whether the C_8–H proton of compound (XI) would show one singlet in place of splitted signal of the compound (XI) freshly prepared after the allowance of XI at room temperature or not. The former attempt was unsuccessfull, but in the latter expectation the same result as the other optically active compounds was obtained (Fig. 4).

The compound (XI) was elucidated as its dipicrate and through formation of XII by acidic hydrolysis of XI. Furthermore, after the compound showing one singlet due to the

Table IV. Optical Rotatory Dispersion

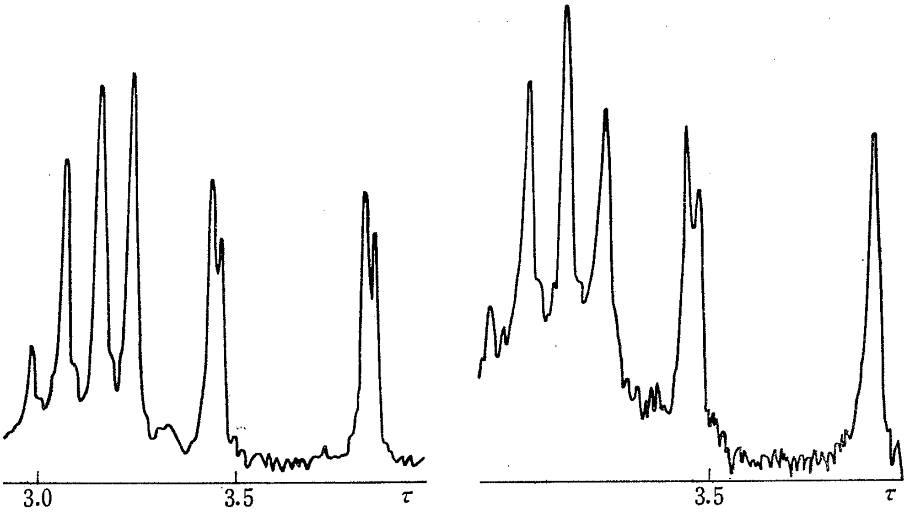
Compound	[ϕ]	λ (mμ)	a	Compound	[ϕ]	λ (mμ)	a
IX (RS)	+ 3810	291 (pk)	+ 18	X (SR)	− 4110	292 (tr)	− 19
(berbamunine)	+ 2000	279 (tr)		(magnoline)	− 2190	279 (pk)	
	+ 9530	250 (pk)			−10750	250 (tr)	
VII (SS)	+16220	297 (pk)	+174	VIII (RR)	−16420	295 (tr)	−173
	− 1200	280 (tr)			+ 920	280 (pk)	
	+13200	262 (pk)	+ 11		−13510	260 (tr)	− 15
	+12120	255 (tr)			−12040	253 (pk)	
	+ 4867	241 (pk)			−48780	240 (tr)	
III (SS)	+15230	293 (pk)	+130	IV (RR)	−14120	293 (tr)	−123
	+ 2210	279 (tr)			− 1830	279 (pk)	
	+ 9820	267 (pk)	+ 13		− 8850	265 (tr)	− 9
	+ 8530	264 (tr)			− 7960	261 (pk)	
	+36940	243 (pk)			−34890	243 (tr)	

molecular rotations and cotton effects; pk=peak; tr=trough

Table V. Circular Dichroism

Compound	θ	λ (mμ)	Compound	θ	λ (mμ)
IX (RS) (berbamunine)	+ 1840	281 (p)	X (SR) (magnoline)	− 1940	282 (n)
	+ 9420	242 (p)		− 9980	242 (n)
VII (SS)	+17810	288 (p)	VIII (RR)	−17500	290 (n)
	− 2010	249 (n)		+ 2260	251 (p)
	+42070	233 (p)		−43040	235 (n)
III (SS)	+13670	288 (p)	IV (RR)	−12600	289 (n)
	− 1980	258 (n)		+ 1810	260 (p)
	+39700	235 (p)		−39510	235 (n)

molecular ellipticites (θ); p=positive maximum; n=negative maximum



A) fresh B) after 37 days

Fig. 4. NMR Spectra of XI ($CDCl_3$, 100 Mc)

C_8–proton had been refluxed in pyridine for 48 hr, the reaction mixture was treated as usual as soon as possible, but there appeared no change regarding the C_8–proton in its NMR spectrum of the product (XI). Accordingly, the bisbenzylisoquinolines having one biphenyl ether linkage, whose hydroxyl groups are protected with benzyl group, seem to be changed in its conformation or chemical structure, while being set aside at room temperature for a long time.

Experimental[11]

Optical rotations were measured on a Yanagimoto photomagnetic direct reading polarimeter OR-10. The ORD and CD curves were determined in methanol–dioxane on a JASCO/UV-5 spectropolarimeter (l=0.01 dm; c=1 mg/ml or less). The NMR spectra were determined on a JNM-4H 100 Mc spectrometer with tetramethylsilane as an internal reference.

Formation of III by Ullmann Reaction between (*S*)(+)-I and (*S*)(+)-II——To a solution of 1.35 g of (*S*)(+)-I[$[\alpha]_D^{15}$ +40.2° (in $CHCl_3$)] and 1.01 g of (*S*)(+)-II in 10 ml of dry pyridine was added a mixture of 0.2 g of Cu powder, 1.2 g of anhydrous K_2CO_3 and 0.07 g of KI, and the mixture was heated in an oil–bath under stirring at 160—170° for 77 hr in a current of N_2. After the solvent had been distilled off *in vacuo*, the residue was dissolved in benzene and an insoluble substance was filtered off. The filtrate was washed with 1% NaOH solution and water, dried over K_2CO_3 and evaporated to give a dark brown syrup, which was chromatographed on silicic acid with $CHCl_3$ and $CHCl_3$–MeOH (50:1) as eluants. Removal of the latter eluate gave 400 mg of III as a brown syrup, whose dipicrate was recrystallised from benzene-*n*-hexane to give a yellowish powder, mp 115—120° (sinters at 110°). *Anal.* Calcd. for $C_{57}H_{58}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 62.53; H, 4.87; N, 8.46. Found: C, 62.81; H, 5.03; N, 8.19.

Formation of VII by Debenzylation of III——A mixture of 150 mg of the above isoquinoline (III), 8 ml of EtOH, and 10 ml of conc. HCl was refluxed on a water–bath in a current of N_2 for 2 hr. After the reaction, the solvent was removed by distillation and the residue was made basic with NH_4OH and extracted with ethylene dichloride. The extract was washed with sat. NaCl solution, dried over Na_2SO_4 and evaporated to give a caramel, whose recrystallisation from $CHCl_3$–*n*-hexane afforded 50 mg of VII as a colorless powder, mp 125—130°. *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot 1/2H_2O$[12]: C, 71.38; H, 6.82; N, 4.63. Found: C, 71.23; H, 6.86; N, 4.51.

Formation of XI by Ullmann Reaction between (*R*)(−)-I and (±)-II——To a solution of 3.6 g (*R*) of (−)-I [$[\alpha]_D^{20}$ −41.8° (in $CHCl_3$)] and 2.7 g of (±)-II in 12 ml of dry pyridine was added a mixture of 0.3 g of CuCl and 1.5 g of anhydrous K_2CO_3. The mixture was heated in an oil bath under stirring at 160—170° for 19 hr in a current of N_2. Further, an additional mixture of 0.2 g of CuCl and 1 g of anhydrous K_2CO_3 was added and the heating was continued for further 30 hr. After the solvent had been distilled off *in vacuo*, the residue was dissolved in benzene and the precipitate was filtered off. The benzene layer was washed with 1% NaOH solution and water, dried over K_2CO_3 and evaporated. The resulting brown syrup was chromatographed on silicic acid with $CHCl_3$, $CHCl_3$–MeOH (50:1) and then $CHCl_3$–MeOH (30:1) as eluants. Removal of the latter eluant gave 1.8 g of XI as a brown syrup, $[\alpha]_D^{15}$ −22.2° (c=0.36, l=0.1 dm, $CHCl_3$), whose dipicrate was recrystallised from benzene–*n*-hexane to give a yellowish powder, mp 118—121° (sinters at 110°). $[\alpha]_D^{15}$ −27.8 (c=0.36, l=0.1 dm, $CHCl_3$). *Anal.* Calcd. for $C_{57}H_{58}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 62.53; H, 4.87; N, 8.46. Found: C, 62.81; H, 4.93; N, 8.19.

Formation of XII by Debenzylation of XI——A mixture of 1.2 g of the compound (XI), 20 ml of EtOH and 30 ml of conc. HCl was refluxed in a current of N_2 for 2.5 hr. The reaction mixture was treated according to the same procedure as above to give 0.7 g of a diastereoisomeric mixture (XII) as a brown caramel, whose recrystallisation from $CHCl_3$–*n*-hexane afforded a colorless powder, mp 114—121° (sinters at 111°). $[\alpha]_D^{15}$ −10.5° (c=0.2, l=0.1 dm, MeOH). NMR (τ) ($CDCl_3$): 7.57 (3H, s, N–$C\underline{H}_3$), 7.50 (3H, s, N–$C\underline{H}_3$), 6.20 (3H, s, $OC\underline{H}_3$), 6.19 (3H, s, $OC\underline{H}_3$), 3.81—2.96 (11H, aromatic protons). *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot 1/2H_2O$[12]: C, 71.38; H, 6.82; N, 4.63. Found: C, 71.77; H, 6.74; N, 4.39.

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[11] All melting points were not correct.

[12] This sample was dried at 50° *in vacuo* on P_2O_5 for 48 hr.