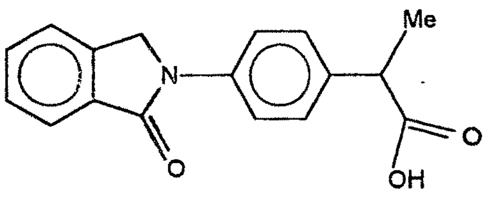
CHAPTER - 4 : PART - I

FORMATION OF (R)- N-[2-(1-HYDROXYBUTYL)] ISOINDOLIN-1-ONE

FORMATION OF (R) N-[2-(1-HYDROXY BUTYL)] ISOINDOLIN-1-ONE

4.1.1 INTRODUCTION

Heterocyclic compounds containing Isoindolin-1-one skeletons have attracted considerable interest in recent years because of their biological activity(1,2). **Indoprofen (1)** an antiinflamatory agent, **Staurosporine (2)** a protein kinase C inhibitor and **pazinaclone** or **DN-2327 (3)** an anxiolytic agent all constitute these class of compounds. Some of the phthalimidine derivatives include inhibitors of thromboxane A_2- induced vaso constrictions(3) and potential antipsychotics (4,5).



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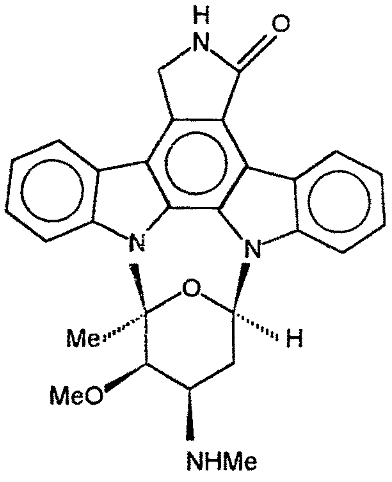

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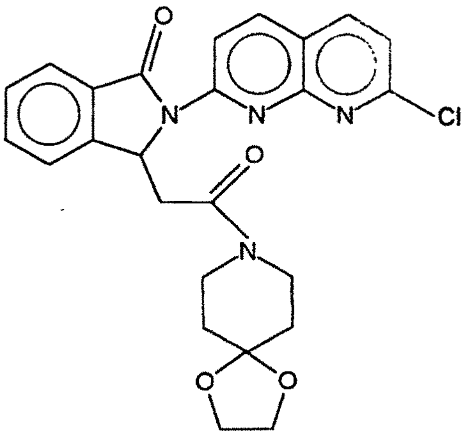

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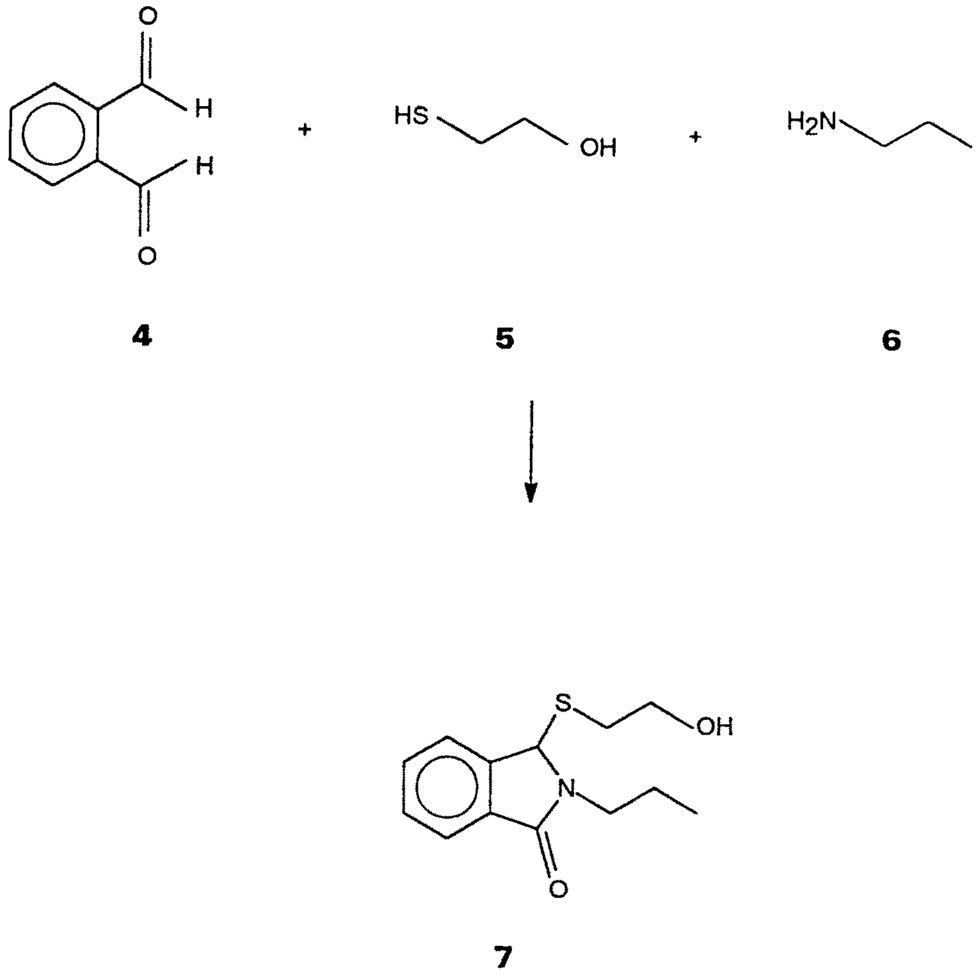
Isoindolin-1-ones or phthalimidines are important synthetic intermediates in the preparation of isoindoles and a few natural products(6,7).

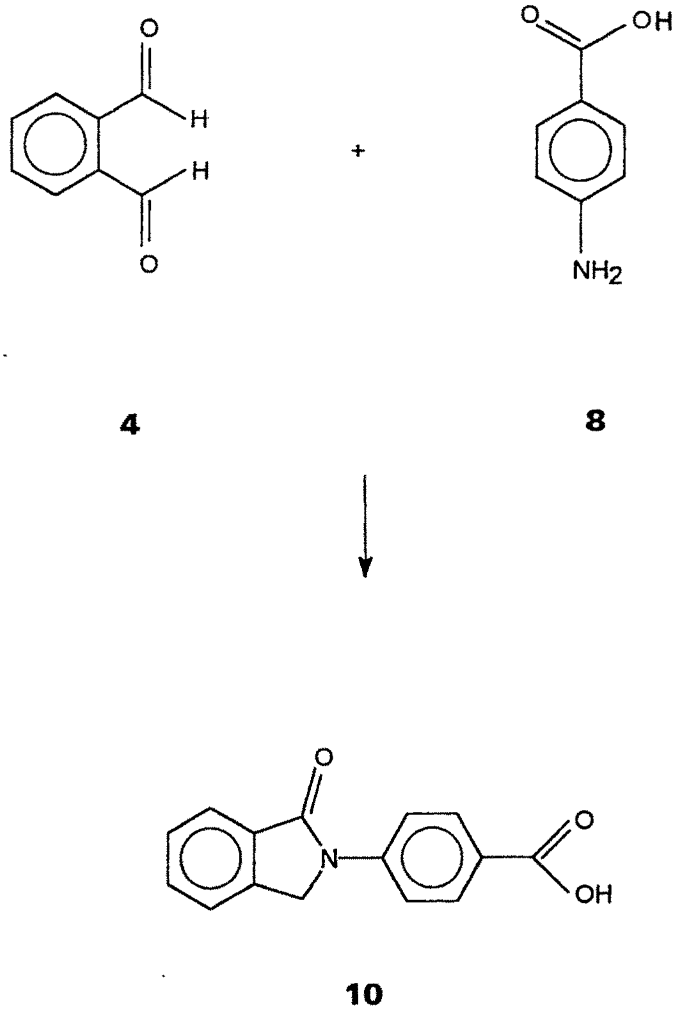
Simons and Johnson(8) studied the reaction of amino acids or proteins with β-mercaptoethanol and o-phthalaldehyde, since the formation of strong fluorescent product allows the detection of smaller amounts of amino acids or proteins which is not possible by other methods. Primary amines, amino acids and proteins react with o-phthalaldehyde and mercaptoethanol to yield the same type of fluorescent products(9). The reaction of o-phthalaldehyde **(4)** with β-mercaptoethanol **(5)** and 1-amino propane **(6)** has been reported to give the corresponding 1-alkylthio-2-alkyl substituted indole(8) **(7)** **(Scheme IV.1.1)**.



Scheme IV.1.1

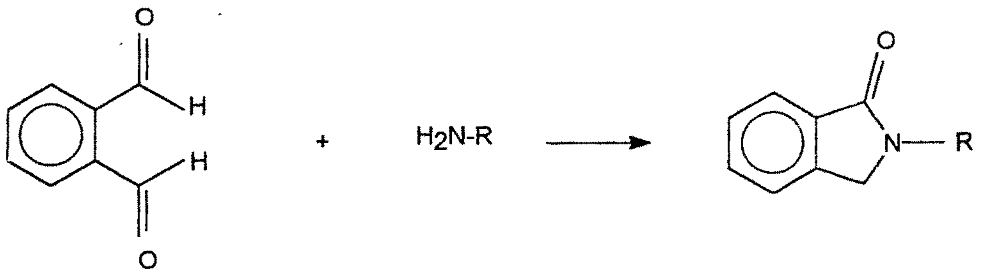
Simons *etal* could not isolate the fluorescent product, so the structure elucidation studies were done in solution. They concluded that the species responsible for fluorescence are isoindoles formed during the reaction.

Tsuruta *etal*(10) also used N-substituted isoindoli-1-one derivates as fluorescent reagents for the derivatization of alcohols. They reported the reaction of o-phthalaldehyde **(4)** with p-aminobenzoic acid **(8)** in ether to furnish the isoindolin-1-one **(10) (Scheme IV.1.2)**.



Scheme IV.1.2

Grigg *etal*(11) reported the synthesis of N-substituted isoindolin-1-ones by the reaction of α- aminoacids and their methyl esters, arylamines, heterocyclic amines, aryl substituted aliphatic amines, with o-phthalaldehyde in the presence of acetic acid **(Scheme IV.1.3)**.

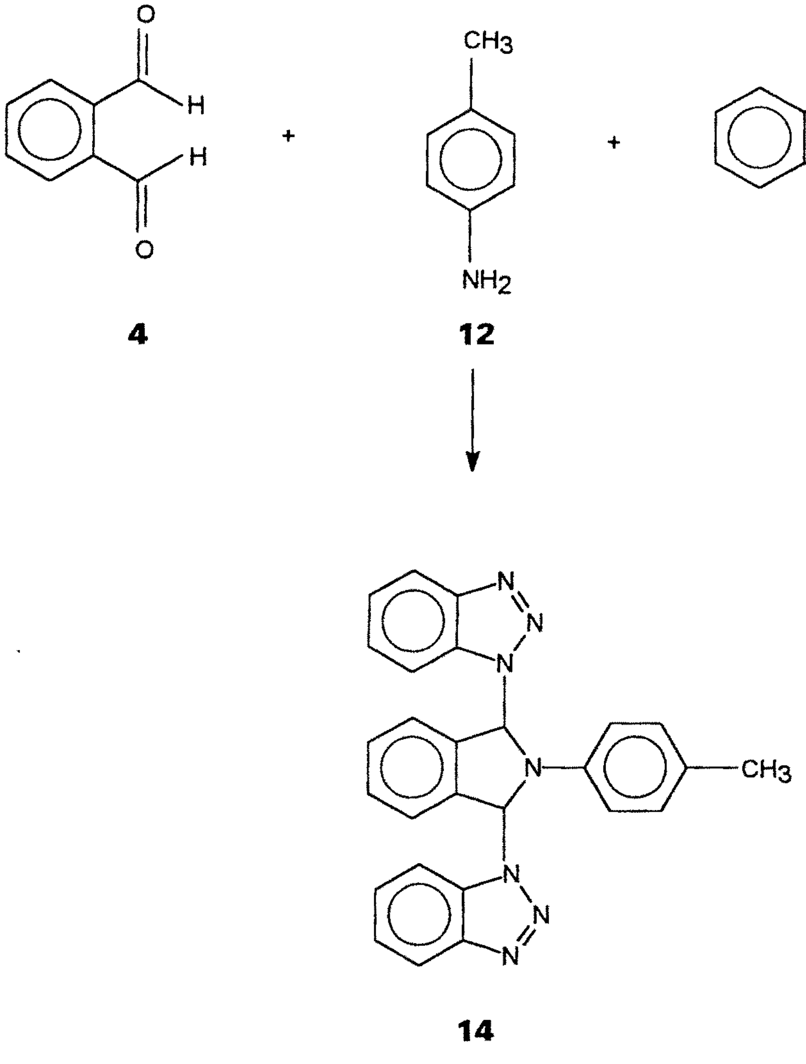


4 **10** **11**

R = $-(CH_2)_3COOH$
C_6H_5-
$C_6H(OCH_3)_4$-
2-thiazolyl-
3-(5-methyl)-isoxazolyl-

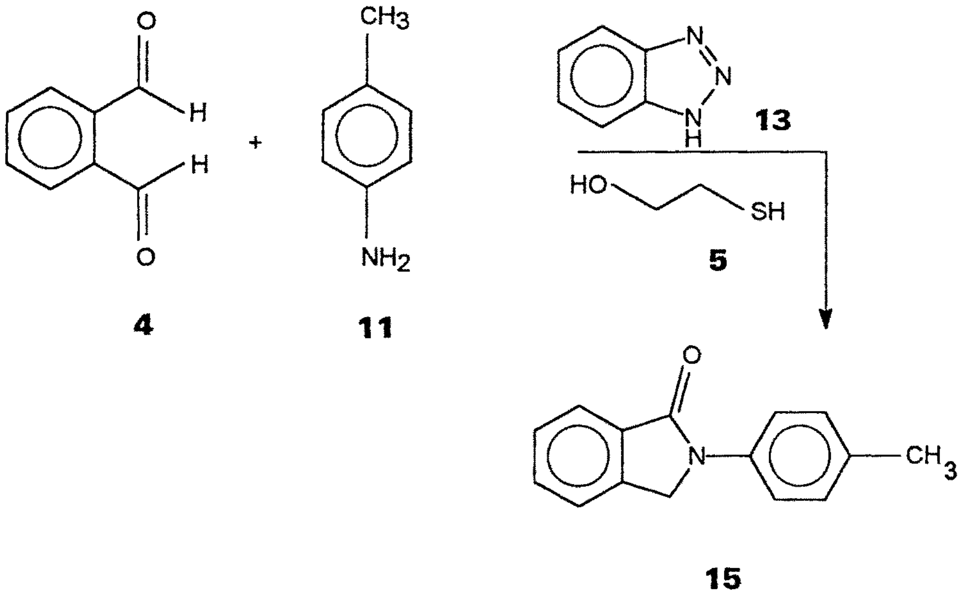
Scheme IV.1.3

Takahashi *etal* (12) reported the double mannich condensation reaction of o-phthalaldehyde **(4)** with p-toluidine **(12)** in the presence of benzotriazole **(13)** to give 1,3-bis (benzotriazolyl) isoindoline **(14)** **(Scheme IV.1.4)**.



Scheme IV.1.4

Takahashi *etal*(13) have recently reported the reaction of o-phthalaldehyde **(4)** with p-toluidine **(11)** in presence of dual synthetic auxiliaries such as benzotriazole **(13)** and mercaptoethanol **(5)** resulting in the formation of 2-(p-tolyl) phthalimidine **(Scheme IV.1.5)**.

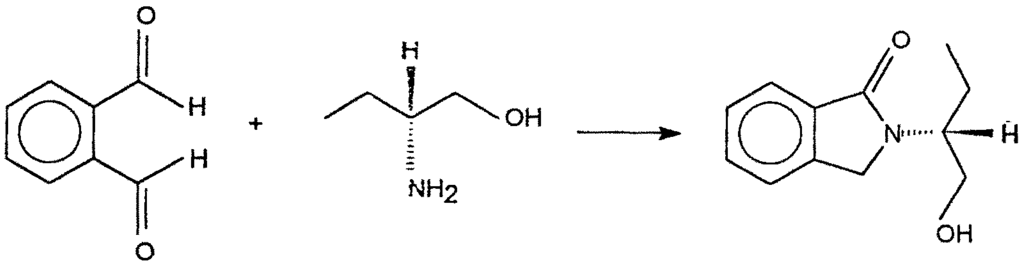


Scheme IV.1.5

This chapter describes the reaction of ***(R)***-(-)-2-amino-1-butanol with o-phthalaldehyde which proceeded in the absence of any synthetic auxiliary or acetic acid as reported by Takahashi *etal*(13) and Grigg *etal*(11) to furnish the N-[2-(1-hydroxybutyl)- isoindolin-1-one].

4.1.2 RESULTS AND DISCUSSION

Equimolar amounts of ***(R)***-(-)-2-amino-1-butanol **(16)** and o-phthaldehyde **(4)** were reacted to furnish the N-[2-(1-hydroxy butyl)-isoindolin-1-one] **(17)** **(Scheme IV.1.6)**.

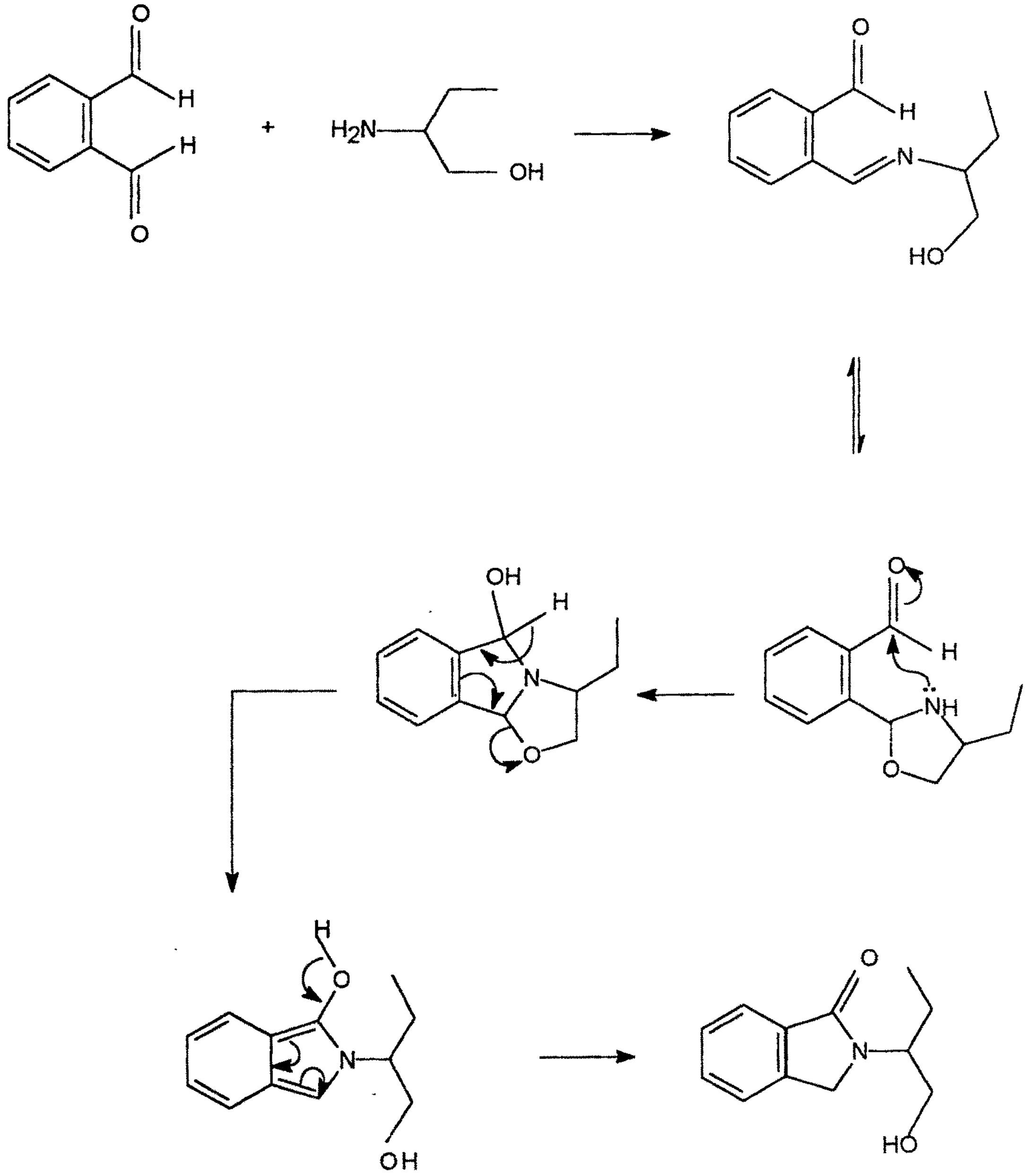


4 **16** **17**

Scheme IV.1.6

The IR spectrum of **17** (Fig. 4.1.I) showed an absorption at 3350 due to the hydroxyl group. The absorption at 1650 cm^{-1} indicated the presence of a carbonyl group of the isoindoline moiety.

The ^1H NMR spectrum of **17** (Fig 4.1.II) showed a triplet at 0.9 δ corresponding to the methyl protons. A multiplet at 1.75 is assigned to the methylene protons. The multiplet at 3.85 - 4.20, accounted for three protons due to -CH-CH_2-O. A quartet appeared at 4.30 - 4.50 is due to the methylene protons characteristic of the ring methylene of the isoindolin-1-one. The aromatic protons appeared at 7.20-7.75 δ. The X-ray diffraction study of **17** was carried out to assign the structure unambiguously. An ORTEP plot is presented (Fig. 4.1.III). A plausible mechanism for the formation of **17** is given below **(Scheme IV.1.7)**.



Scheme IV.1.7

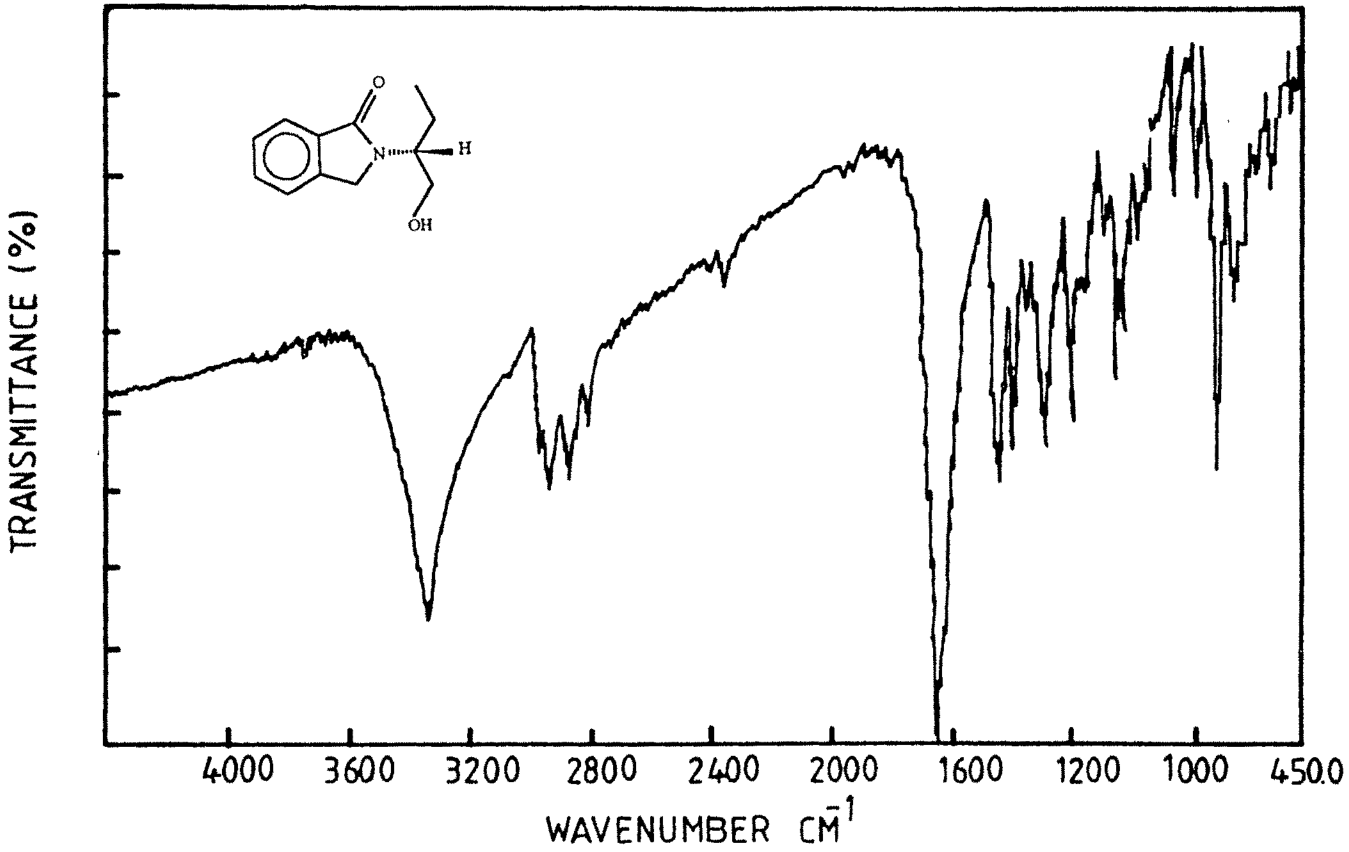


Fig. 4.1.I IR (KBr) spectrum of ***(R)***N-[2-(1-hydroxybutyl) isoindolin-1-one]. **(17)**

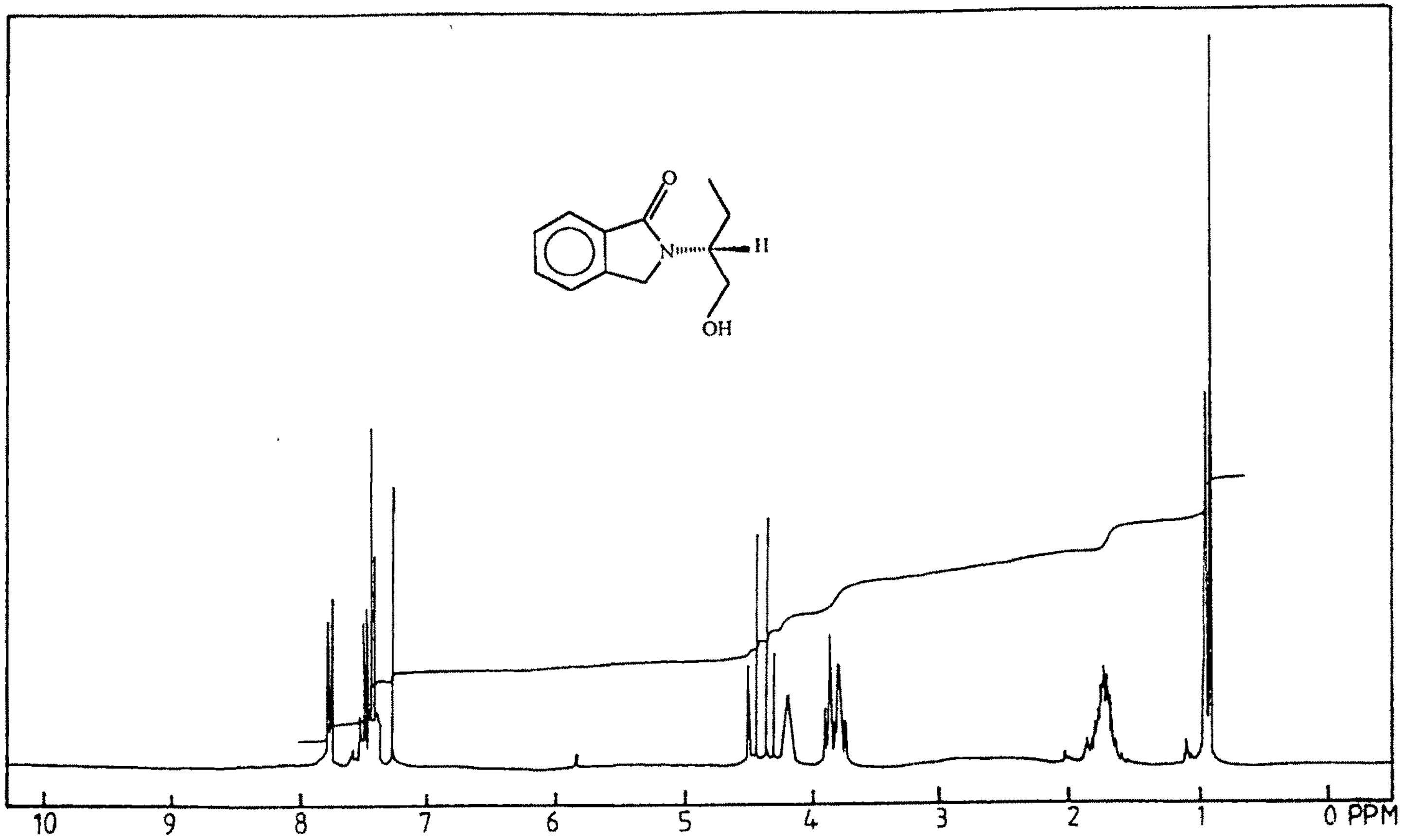


Fig. 4.1.II ¹HNMR ($CDCl_3$) spectrum of ***(R)***N-[2-(1-hydroxybutyl) isoindolin-1-one].
(17)

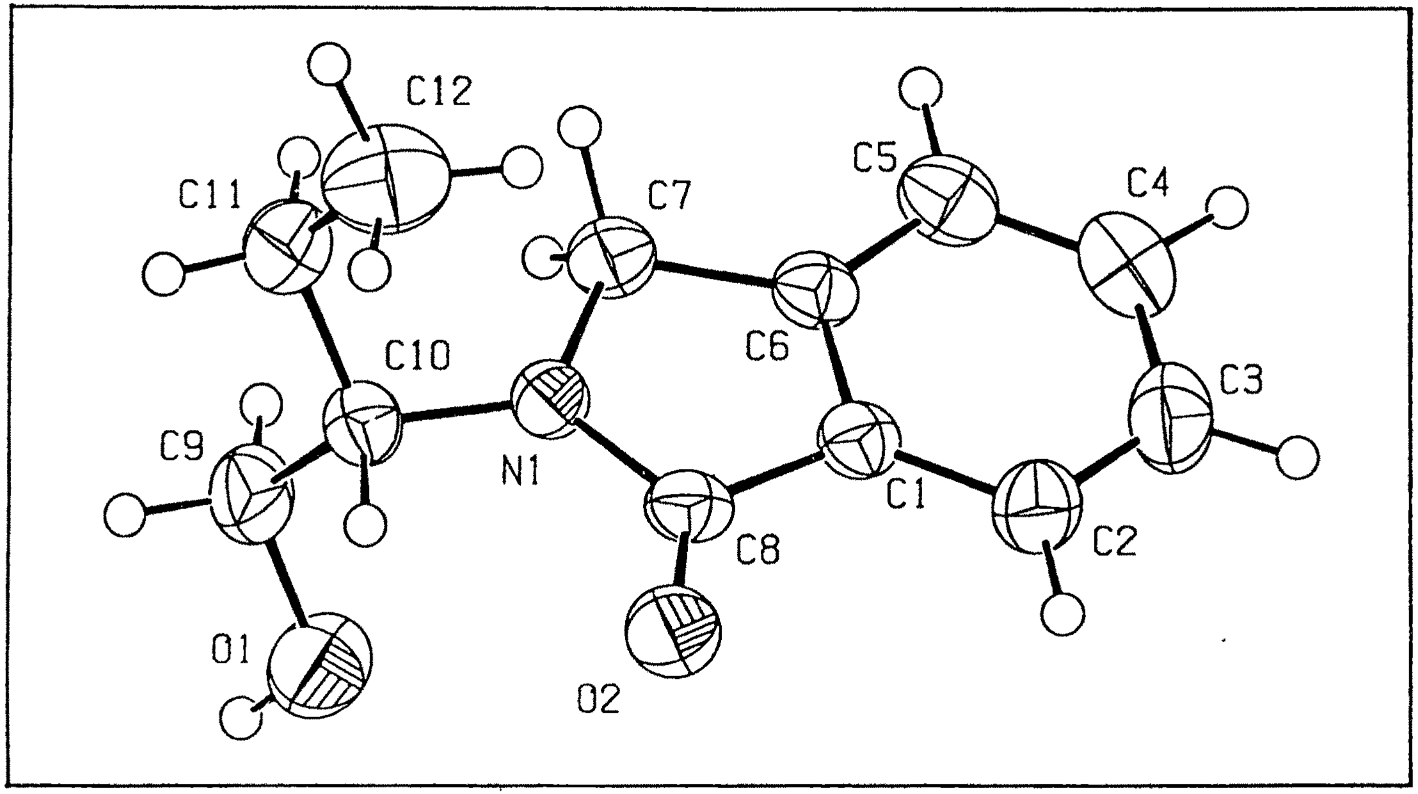


Fig. 4.1.III ORTEP plot of *(R)*N-[2-(1-hydroxybutyl) isoindolin-1-one]. **(17)**

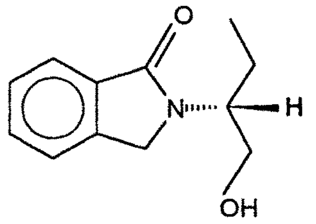
4.1.3 EXPERIMENTAL

An Enraf-Nonius CAD-4 single crystal X-ray diffractometer was used for X-ray crystallographic studies. Mass spectra was performed on a Shimadzu QP-2000. ^{1}H NMR spectra was recorded on a Jeol GSx-270 FT NMR. Chemical shifts are relative to tetramethyl silane. The IR spectrum was recorded on a Shimadzu IR-408 spectrophotometer. Optical rotation was measured on a Jasco-Dip-370 polarimeter. Elemental Analysis was carried out on a Coleman instrument. Melting point was determined on a Gallenkamp-350 micromelting apparatus.

(R) N-[2-(1-hydroxy butyl)] isoindolin-1-one (17)

(R) (-)-2-amino-1-butanol **(16)** (5m.mol) was dissolved in methanol (10ml). The solution was cooled in an ice bath. A solution of o-phthalaldehyde **(4)** (5.m.mol) was added with constant stirring. After 1 hr. the reaction mixture was brought to room temperature. Removal of solvent under reduced pressure gave a residue, which was chromatographed on sillicagel to funish the ***(R)*** N-[2-(1-hydroxy butyl)] isoindolin-1-one **(17)**.

(R) N-[2-(1-hydroxy butyl)] isoindolin-1-one (17)



Yield	: 32%	M.P.	: 139°C

CHN found (calculated) : C - 70.11 (70.24), H - 6.96 (7.31), N - 6.77 (6.82).

$[\alpha]_D^{25}$: +31.87° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3350,2900,1650,1470,1450,1300 and 1220.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.75 (2H,m,-CH_2) 3.85-4.20 (3H,m,-CH-CH_2-O), 4.30-4.50 (2H,m,methylene proton on the 5 membered ring), 7.20 - 7.75 (4H,m,-C_6H_4).

m/z : 205(M^+), 174,160,146,134,119,104,91,77,65.

CRYSTAL DATA AND STRUCTURE REFINEMENT

Crystal data for **17** : $C_{12}H_{15}NO_2$, *M* 205.25, Crystal size 0.4 x 0.2 x 0.15 mm^3. T = 293 (2) K, Crystal system : orthorhombic, Space group $P2_1\,2_1\,2_1$, *a*=5.776 A°, *b*=12.599 A°, *c*=15.288 A°, *U*=1112.5 A^3, Z=4 , D*c* 1.225 mg/m^3, μ=0.083 mm^{-1}, F(000) - 440, λ (Mo-K_α) = 0.71073 A°.

A crystal of **17** was mounted on glass fiber and intensity data was measured using the small Mar research plate scanner and Mo radiation. 95 frames were measured with a 2° rotation and an exposure time of 3 min per frame. Data were processed with the Mar version of the XDS package, to give 6928 reflections. 1150 were unique with a merging R of 5.13% 14 reflections were rejected, leaving 1136. θ range for data collection 2.09 to 24.91° index ranges $0 <= h <= 6$, $0 <= k <= 14$, $0 <= l <= 18$.

The structure was solved(14) by direct methods using SHELX-86 and refined with SHELXL. The final conventional R factor is 4.05% based on 1051 observations for which $Fo>4\sigma(Fo)$ and 5.47% for all 1136 data. The refinement method was full martrix least squares on F^2. Goodness of fit on F^2 was 1.140. The absolute structure parameter of flack as implemented in the package refined to a value of 0.2205 (0.1054). The largest difference peak and hole in the final map were 0.124 and $-0.125eA^{-3}$.

Tables of atomic coordinates, anisotropic displacement parameters, bond lengths and angles are also presented. (Tables IV.I.I - IV.I.IV)

Table IV.I.I.

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 17. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	3499(4)	1229(2)	6218(2)	36(1)
C(2)	2663(5)	527(2)	5579(2)	49(1)
C(3)	3925(6)	425(2)	4809(2)	56(1)
C(4)	5996(6)	991(2)	4687(2)	56(1)
C(5)	6825(5)	1684(2)	5330(2)	50(1)
C(6)	5523(4)	1805(2)	6091(2)	38(1)
C(7)	5907(4)	2532(2)	6865(2)	42(1)
C(8)	2518(4)	1508(2)	7094(2)	37(1)
C(9)	2879(5)	3973(2)	8147(2)	52(1)
C(10)	3535(5)	2805(2)	8279(2)	40(1)
C(11)	5651(5)	2686(2)	8877(2)	53(1)
C(12)	6268(8)	1532(3)	9075(3)	77(1)
N(1)	3930(3)	2278(2)	7433(1)	38(1)
O(1)	816(4)	4034(2)	7642(2)	70(1)
O(2)	793(3)	1129(2)	7459(1)	53(1)

Table IV.I.II

Anisotropic displacement parameters (A^2 x 10^3) for 17.The anisotropic displacement factor exponent takes the form :

$-2 \pi^2$ [$h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}$]

	U11	U22	U33	U23	U13	U12
C(1)	34(1)	28(1)	47(1)	0(1)	-2(1)	3(1)
C(2)	49(2)	38(1)	58(2)	-5(1)	-3(2)	-1(1)
C(3)	70(2)	49(2)	51(2)	-11(1)	-5(2)	9(2)
C(4)	63(2)	52(2)	53(2)	0(1)	12(2)	9(2)
C(5)	47(2)	47(2)	56(2)	7(1)	9(1)	3(1)
C(6)	35(1)	34(1)	45(1)	3(1)	0(1)	4(1)
C(7)	35(1)	41(1)	50(1)	-2(1)	5(1)	-8(1)
C(8)	29(1)	31(1)	50(1)	2(1)	1(1)	0(1)
C(9)	57(2)	40(1)	58(2)	-9(1)	-6(2)	7(1)
C(10)	39(1)	37(1)	44(1)	-4(1)	1(1)	1(1)
C(11)	53(2)	59(2)	46(2)	-5(1)	-6(1)	2(2)
C(12)	75(2)	75(2)	82(2)	22(2)	-14(2)	12(2)
N(1)	33(1)	33(1)	46(1)	-4(1)	3(1)	-4(1)
O(1)	68(1)	52(1)	90(2)	-11(1)	-29(1)	17(1)
O(2)	43(1)	49(1)	68(1)	-9(1)	13(1)	-14(1)

Table IV.I.III

Bond lengths [A^0] for 17.

C(1)-C(2)	1.403(4)	N(1)-C(7)	1.469(3)
C(2)-C(3)	1.391(4)	N(1)-C(8)	1.369(3)
C(3)-C(4)	1.405(5)	N(1)-C(10)	1.471(3)
C(4)-C(5)	1.399(4)	C(8)-O(2)	1.238(3)
C(5)-C(6)	1.394(4)	C(9)-O(1)	1.422(4)
C(6)-C(1)	1.389(3)	C(9)-C(10)	1.533(4)
C(1)-C(8)	1.496(4)	C(10)-C(11)	1.534(4)
C(6)-C(7)	1.513(3)	C(11)-C(12)	1.527(5)

Table IV.I.IV

Bond Angles (°) For 17.

C(1)-C(2)-C(3)	117.9(3)	O(2)-C(8)-N(1)	125.6(2)
C(2)-C(3)-C(4)	120.7(3)	O(2)-C(8)-C(1)	128.1(2)
C(3)-C(4)-C(5)	121.0(3)	N(1)-C(8)-C(1)	106.3(2)
C(4)-C(5)-C(6)	118.0(3)	C(8)-N(1)-C(7)	113.1(2)
C(5)-C(6)-C(1)	120.9(2)	C(8)-N(1)-C(10)	124.0(2)
C(6)-C(1)-C(2)	121.4(2)	C(7)-N(1)-C(10)	122.8(2)
C(6)-C(1)-C(8)	108.7(2)	O(1)-C(9)-C(10)	109.3(2)
C(2)-C(1)-C(8)	129.9(2)	N(1)-C(10)-C(9)	110.8(2)
C(1)-C(6)-C(7)	109.3(2)	N(1)-C(10)-C(11)	110.9(2)
C(5)-C(6)-C(7)	129.8(2)	C(9)-C(10)-C(11)	111.7(2)
N(1)-C(7)-C(6)	102.5(2)	C(10)-C(11)-C(12)	113.4(3)

4.1.4 REFERENCES

1. Funato N, Takayanagi H, Konda Y, Toda Y & Harigaya Y. ***Tetrahedron lett.***, **35** (1994) 1251.
2. Link J T, Raghavan S & Danishefsky S J. ***J. Am. Chem. Soc.***,**117** (1995) 552.
3. Kato Y, Ebiike H, Achiwa K, Ashizawa N, Kurihara T & Kobayashi F. ***Chem. pharm. Bull.***, **38** (1990) 2060.
4. Norman M H, Rigdon G C, Navas F & Cooper B R. ***J. Med. Chem.***, **37** (1994) 2552.
5. Norman M H, Minick D I & Rigdon G C. ***J. Med. Chem.***, **39** (1996) 149.
6. White J D & Mann M E, ***Advances in Heterocyclic chemistry***, **10** (1969) 113.
7. Brener E & Zbaida S, ***Tetrahedron.*** , **31** (1975) 499.
8. Stoney Simons Jr. S & Johson David F, ***J. Am. Chem. Soc.***, **78** (1976) 7098.
9. Benson J R & Hare P E, ***Proc. Natl. Acad. Sci. USA.***, **72** (1975) 619.
10. Tsurutu Yasuhito & Kobashi Kazyya, ***Jap. Kokai***, 62, 198, 658, (1987) : ***CA*** **108** (1988) 204488 y.
11. Grigg Ronald, Gunaratne Nirmal H Q & Visuvanthar Sridharan, ***J. Chem. Soc. Chem. Commun.***, (1985) 1183.
12. Takahashi I, Tsuzuki M, Yokota H, Morita T, Kitajima H & Isa K. ***Heterocycles.***, **43** (1996) 71.
13. Takahashi I, Kawakami T, Hirano E, Yokota H & Kitajima H, ***Synlett.***, (1996) 353.
14. Kabsch W. ***J. Appl. Cryst.***, **26** (1993) 795.

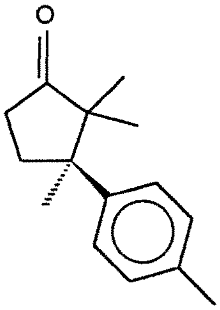
CHAPTER - 4 : PART - II

Formation of A Novel Chiral Ring System

FORMATION OF A NOVEL CHIRAL RING SYSTEM

4.2.1 INTRODUCTION

Chiral quaternary carbon compounds prepared from bicyclic lactams are of high synthetic utility(1). Several natural products have been reported to be prepared using this methodology in high enantlomeric purity. Meyers *etal* reported the synthesis of **(-)-(α)-Cuparenone**(2) **(1)**, **(-)Grandisol**(3) **(2)**, and **Siliphiperfol-6-ene**(4) **(3)** making use of the bicyclic lactams.



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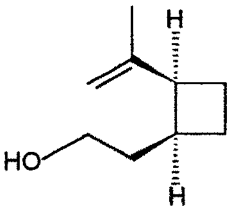

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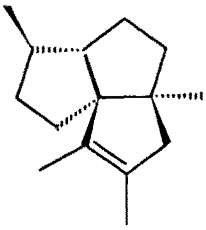

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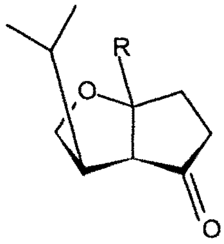
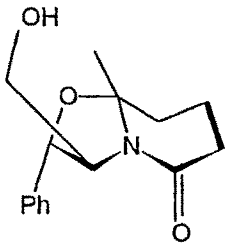
Some of the bicyclic lactams **(4-6)** which are of high synthetic potential are shown below :



R = Me, Ph

4



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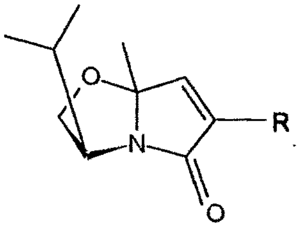
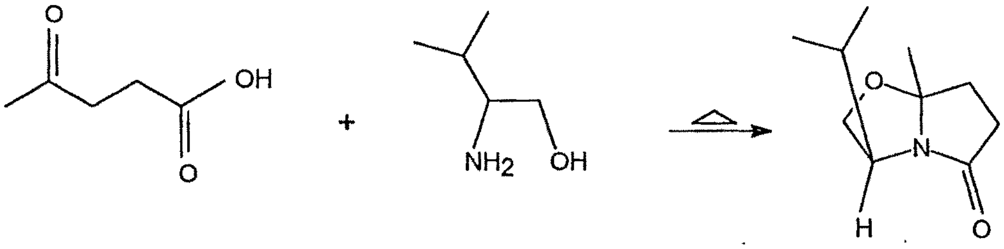


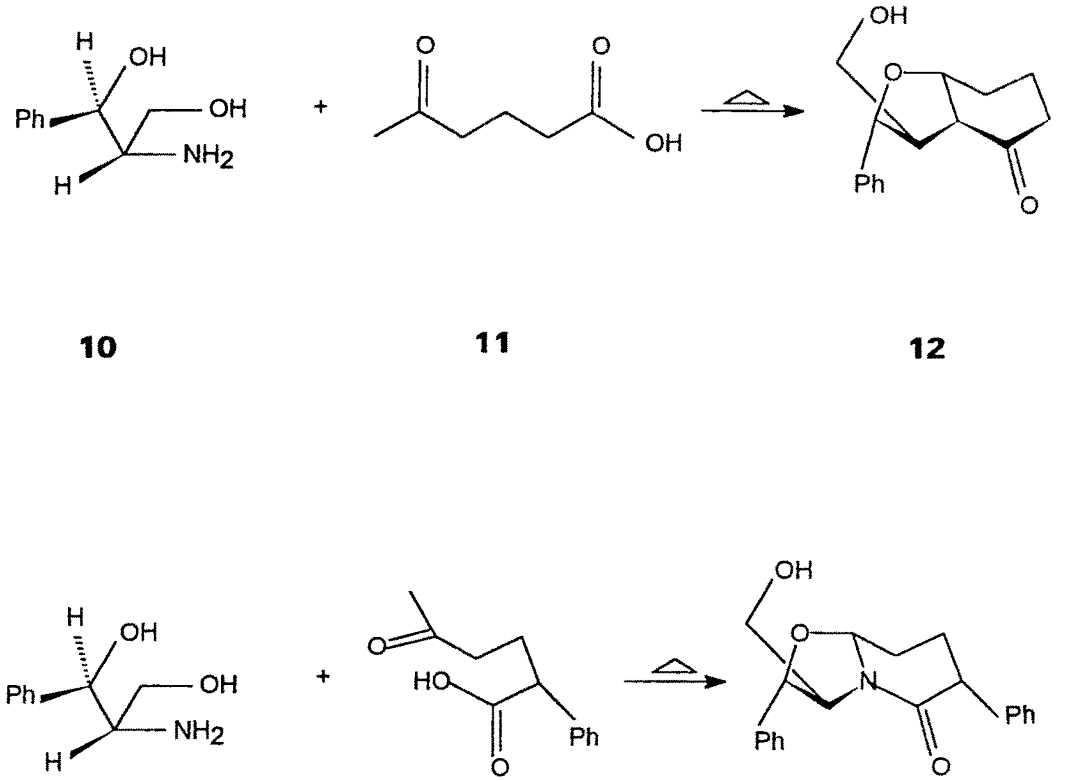
R = Me, Ph

6

The bicylic lactams may be prepared by the cyclodehydration of chiral amino alcohol with γ and δ keto acids(5) **(Scheme IV.2.1)**.



7 **8** **9**

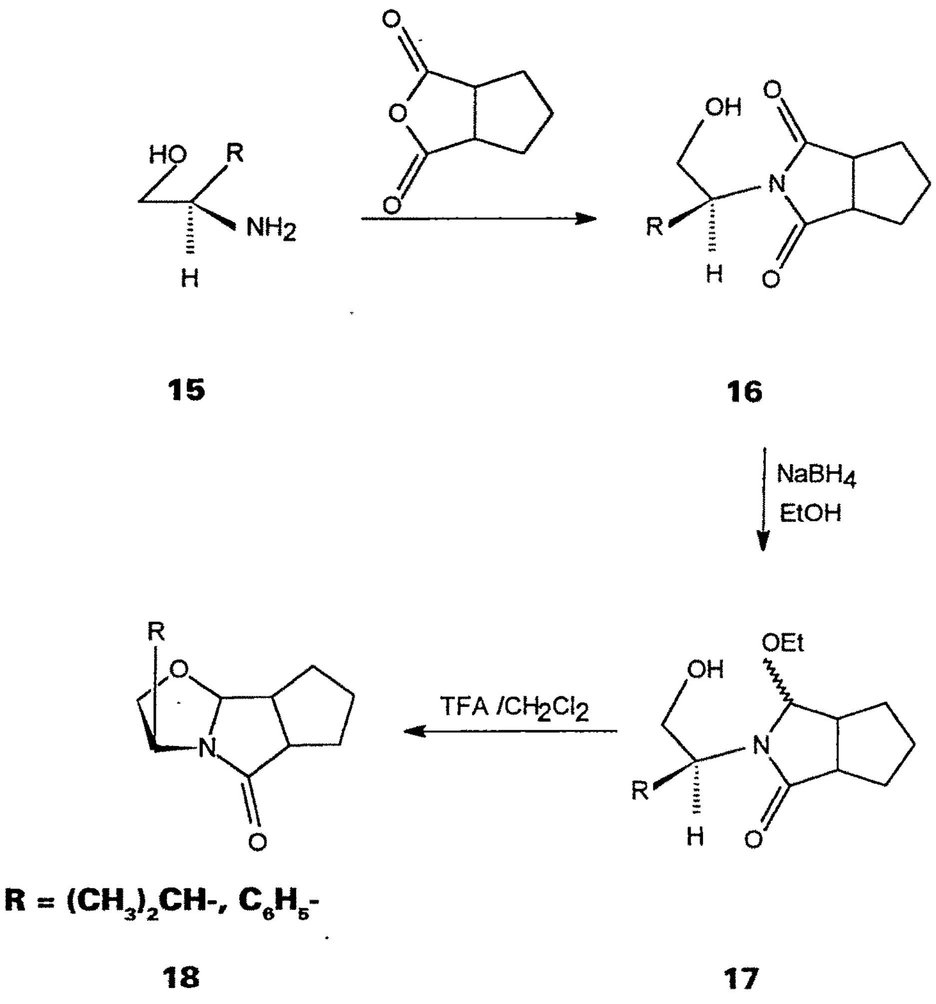


10 **11** **12**

10 **13** **14**

Scheme IV.2.1

Meyers *etal*(6) have reported the preparation of bicyclic lactams, from acyl iminium ions, which is derived from 2-alkoxy amines. The 2-alkoxy amines were prepared by the sodium borohydride reduction of imides **(Scheme IV.2.2)**.

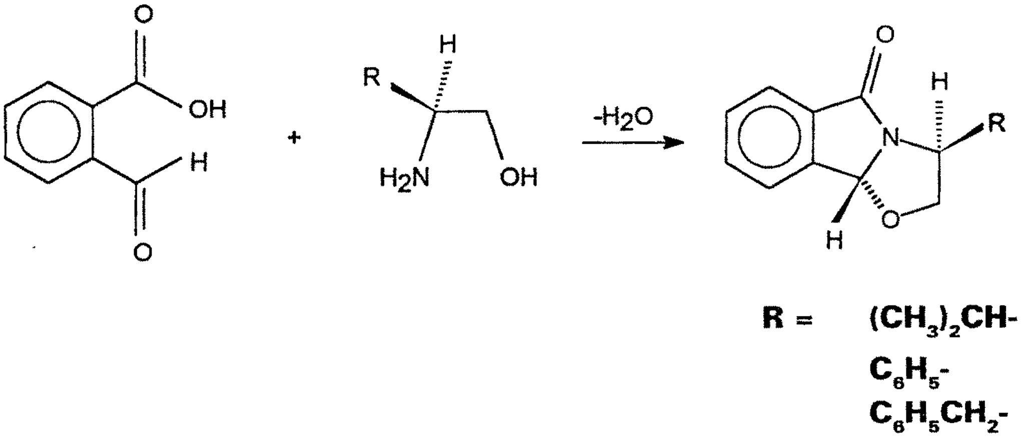


R = $(CH_3)_2CH$-, C_6H_5-

Scheme IV.2.2

There have been several attempts to design isosteres of β lactams which are not four membered rings. Most of these mimics have been γ lactams, particularly pyrazolidinones, imidazolidinones and hydantoins(7).

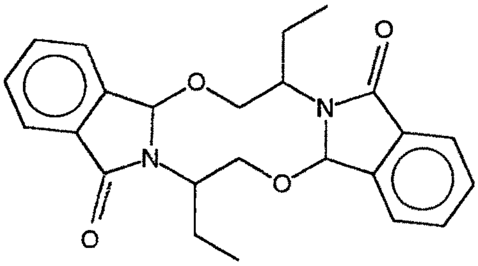
Recently Steven *etal*(8) have synthesised a tricyclic lactam **(21)** by the reaction of 2-formyl benzoic acid **(19)** with β amino alcohols **(20)** **(Scheme IV.2.3)**.



19 **20** **21**

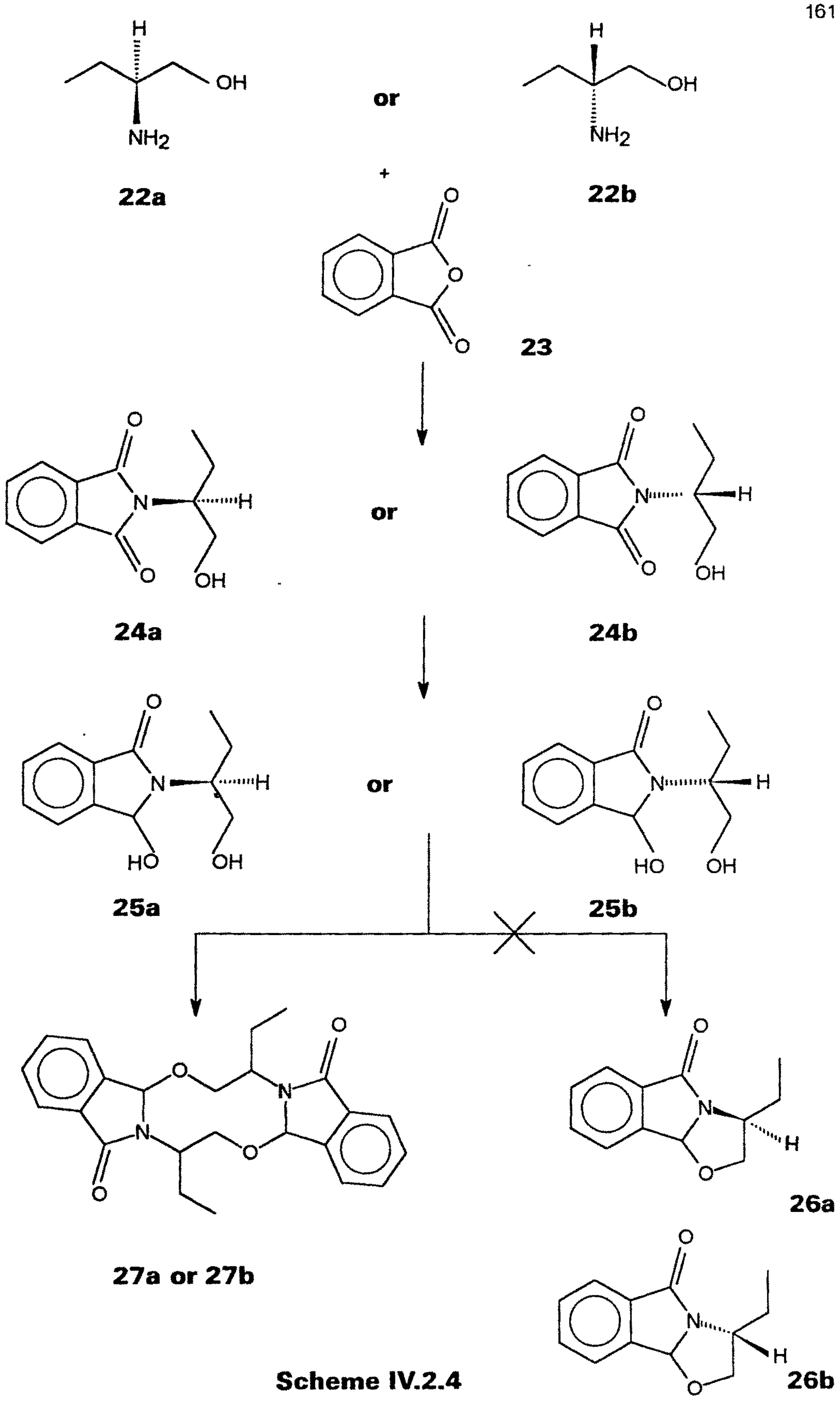
Scheme IV.2.3

This chapter describes an attempt to prepare a tricyclic γ-lactam using Meyer's methodology(6). but it yielded a hitherto unknown ten membered ring system with four chiral centres.



4.2.2 RESULTS AND DISCUSSION

(S) or ***(R)*** 2-amino-1-butanol **(22a or 22b)** were reacted with phthalic anhydride **(23)** to furnish the phthalimides of 2-amino-1-butanol **(24a or 24b)**. The phathalimides were reduced with sodium borohydride in methanol or methanolic HCl. Meyers *etal*$^{(6)}$ reported that the reduction of the imides in alcohol furnished the corresponding alkoxy derivatives. We have reduced the phthalimides **24a & 24b** with sodium borohydride in methanol resulting in the formation of the hydroxy derivatives **(25a and 25b)** and not methoxy derivatives as reported by Meyers *etal*$^{(6)}$. **(24a and 24b)** were subjected to acid catalyzed cyclisation (trifluoroacetic acid in dichloromethane) with an expectation that they would undergo an intramolecular cyclization to furnish **26a & 26b**, instead it has undergone an intermolecular cyclization to yield **27a & 27b** which was found to be an hitherto unknown ten membered heterocyclic fused ring system with four chiral centres **(Scheme IV.2.4)**.


22a
or
22b
+
23
24a
or
24b
25a
or
25b
27a or 27b
26a
26b
OH
NH2
H
N
O
HO

Scheme IV.2.4

The ^1H NMR spectrum of **24a** (Fig. 4.2.I) showed a triplet at 0.9 corresponding to the methyl group. A multiplet at 1.9 is assigned to the methylene group. The multiplet at 3.8 is assigned to $-CH_2-CH_2-O$. A singlet at 5.3 is due to the hydroxyl group. Aromatic protons showed singlet at 7.5 δ.

24a on reduction with sodium borohydride gave the hydroxy derivative **25a**. The ^1H NMR spectrum of **25a** (Fig. 4.2.II) showed a multiplet at 0.9 due to the methyl protons. A multiplet at 1.7 is due to the methylene protons. The multiplet at 3.5 - 4.2 corresponds to $-CH_2-CH_2-O$. The doublet at 5.8 is due to the -CH proton of the five membered ring. The aromatic protons appeared at 7.4 δ.

The ^1H NMR spectrum of **27a** (Fig. 4.2.III) showed a triplet at 0.9 accounted for 6H, is assigned to the two methyl groups. The multiplet at 1.8 corresponds to the methylene protons. The triplet at 3.5 is due to the $-CH_2-O$ protons. The singlet at 6.0 accounted for two protons is due to the -CH protons of the five membered rings. The multiplet at 7.8 δ corresponds to the C_6H_4- protons.

27a is subjected to single crystal X-ray diffraction. The absolute configuration of **27a** is found to be ***(2S*, 11R*, 14S*, 23R*)***. The ORTEP plot of **27a** is presented in (Fig. 4.2.IV). The unit cell parameters and basic information about data collection and structure refinement are summarised in experimental section. A crystal packing diagram of **24a** is also presented (Fig. 4.2.V).

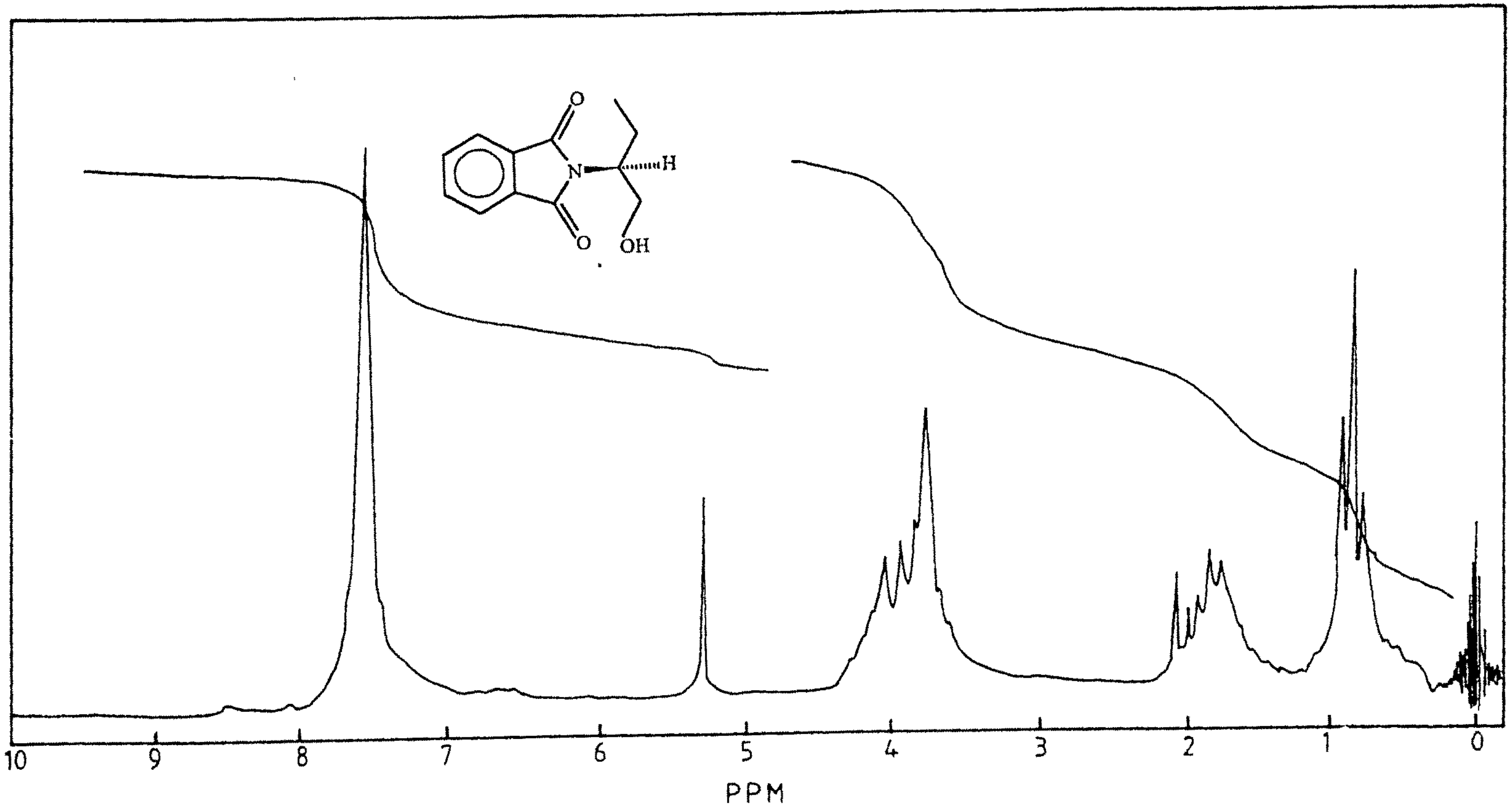


Fig. 4.2.I ^{1}H NMR spectrum of ***(S)*** 2-(1-hydroxybutyl) phthalimide. **(24a)**

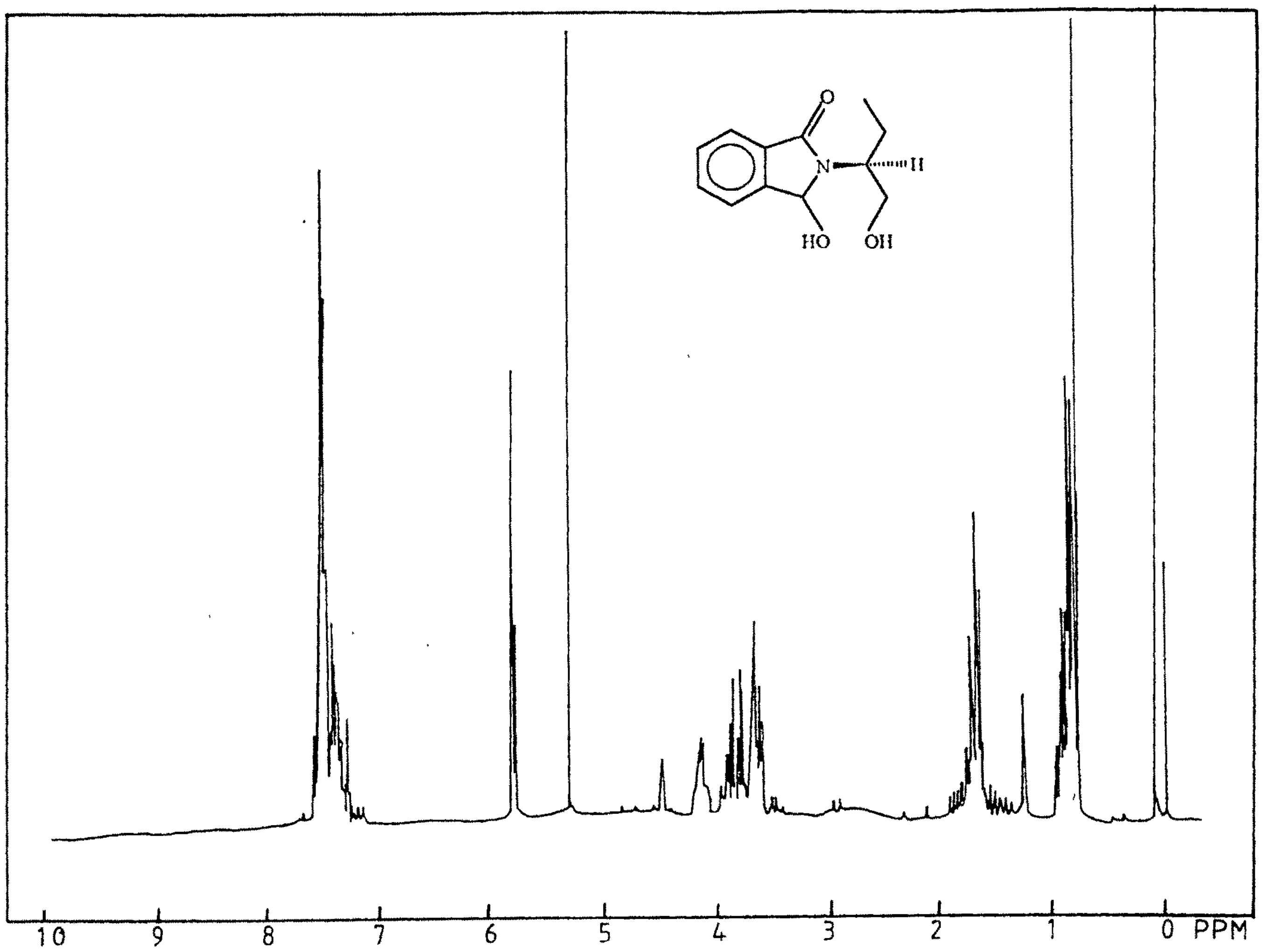


Fig. 4.2.II ¹H NMR spectrum of ***(S)*** 3-hydroxy-2-(1-hydroxybutyl) isoindolin-1-one. **(25a)**

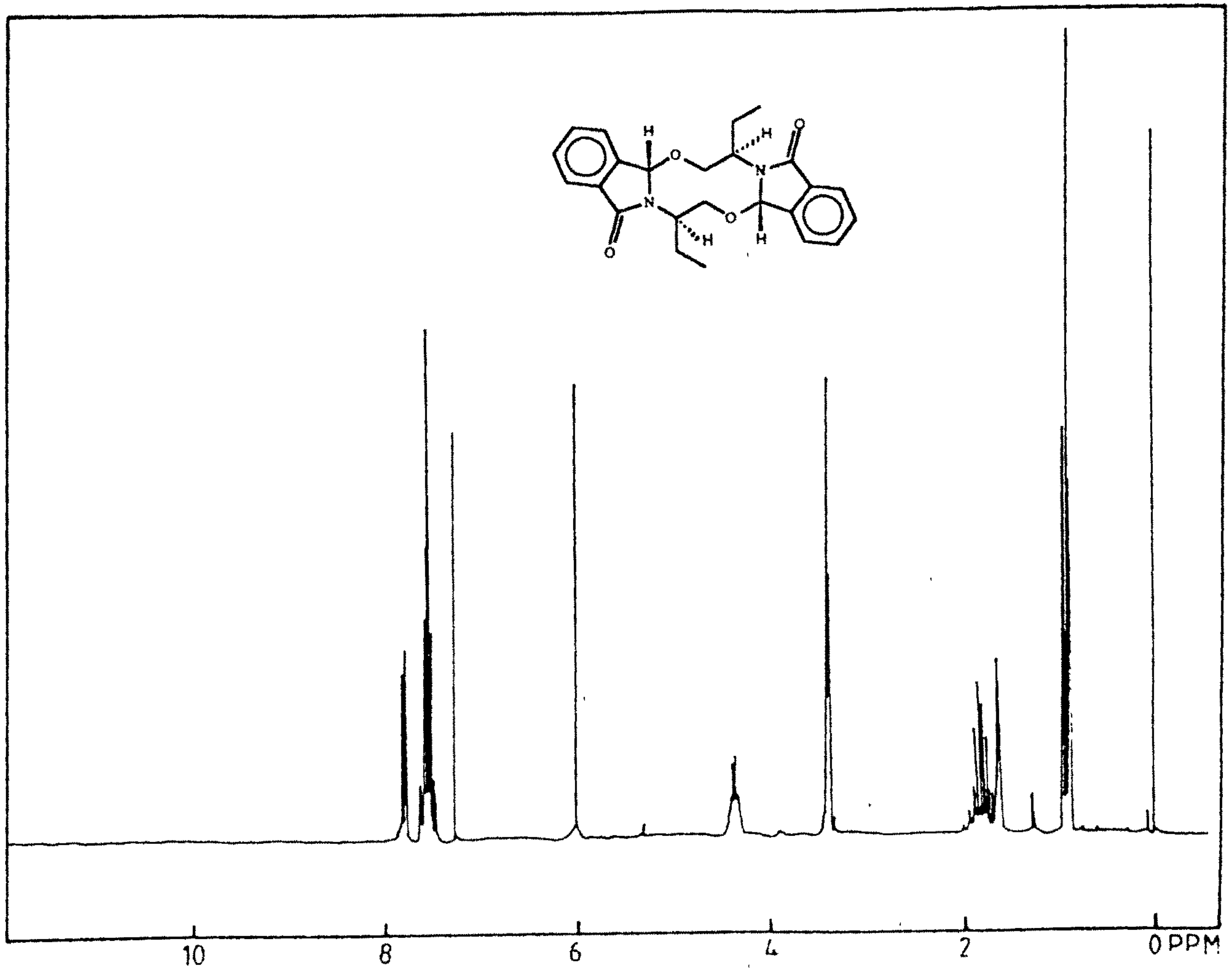


Fig. 4.2.III ¹H NMR spectrum of the chiral ten membered fused ringed system. **(27a)**

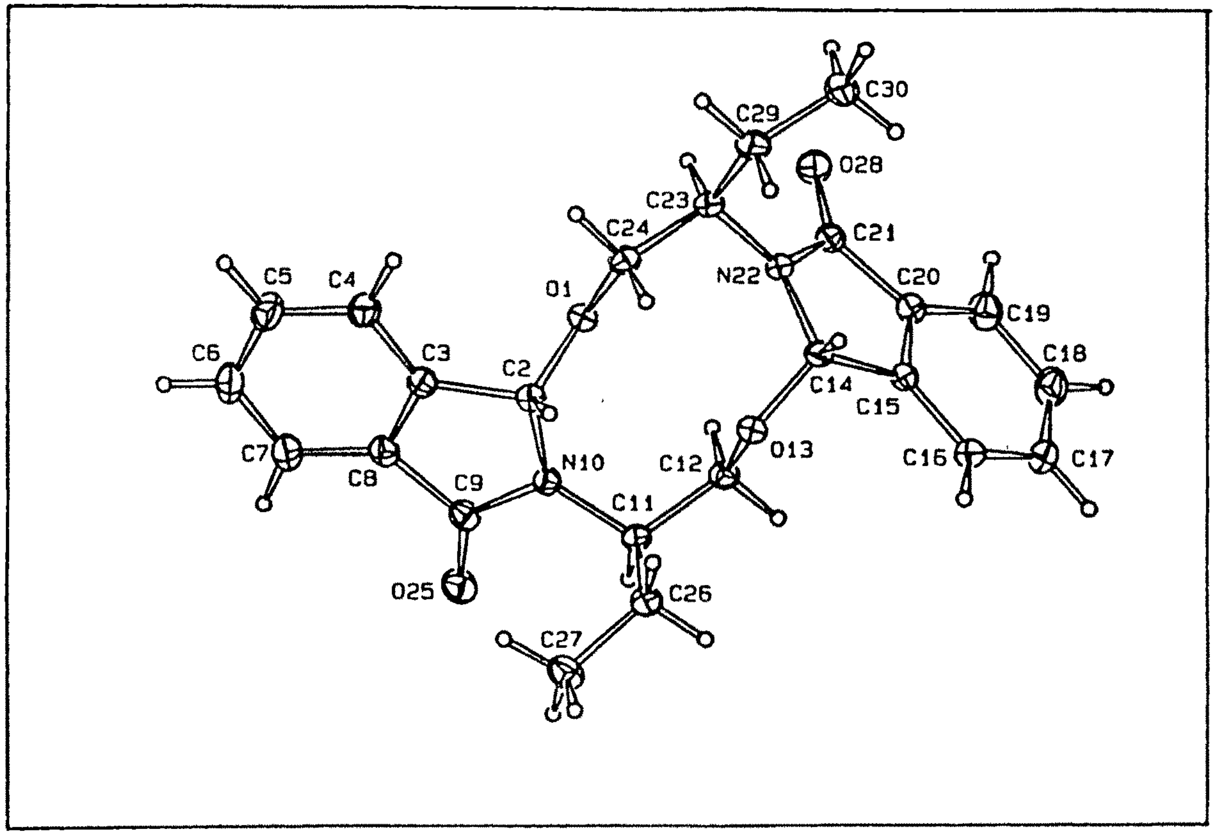


Fig. 4.2.IV ORTEP plot of chiral ten membered fused ring system. **(27a)**

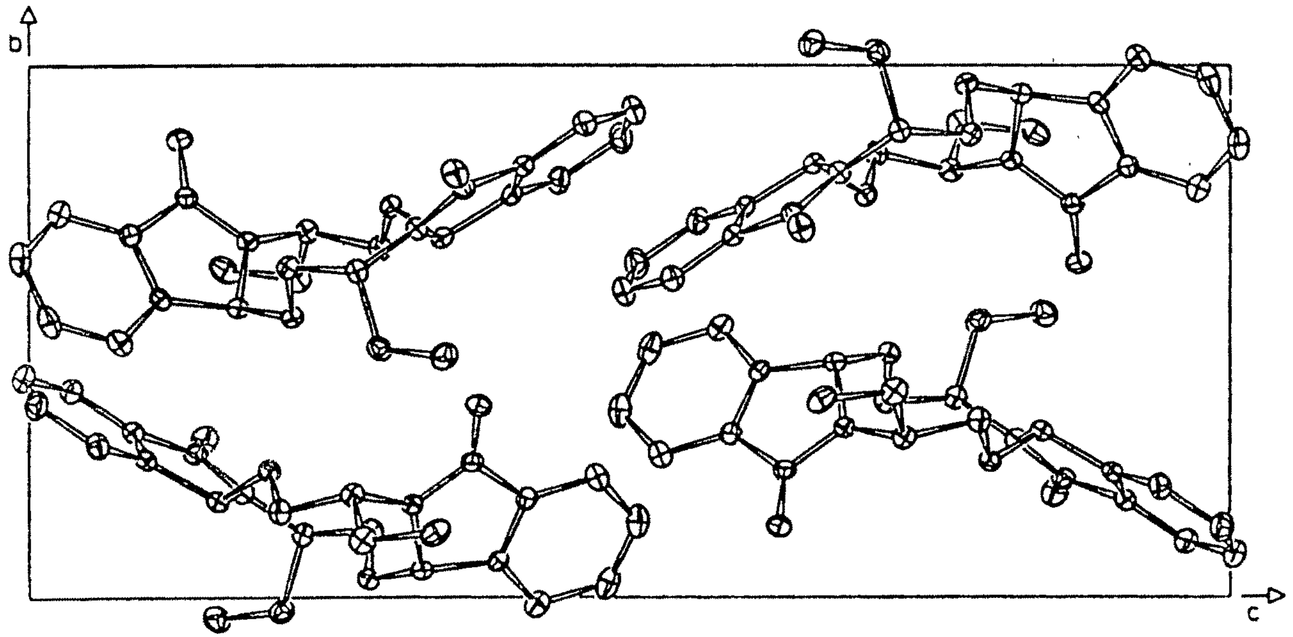


Fig. 4.2.V Crystal packing diagram of **27a**

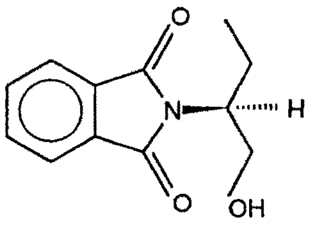
4.2.3 EXPERIMENTAL

A Siemens P.4 single crystal X-ray diffractometer was used for X-ray crystallographic studies. ^{1}H NMR spectra were recorded on a Bruker dpx - 200. Chemical shifts are relative to tetramethylsilane. The infrared spectra were recorded on a Shimadzu IR - 408 spectrophotometer. Optical rotations were measured on a Jasco-Dip-370 polarimeter. Elemental analyses were performed on a Coleman instrument. Melting points were obtained on a Gallenkamp-350 micro melting apparatus by open capillary method and are uncorrected.

4.2.3.1 2-(1-hydroxybutyl) phthalimides 24a & 24b.

(S) or ***(R)*** 2-amino-1-butanol **(22a or 22b)** (0.02 moles) and phthalic anhydride **(23)** (0.02 mole) were mixed separately in an R.B. flask and heated at 140°C for 1hr. After 1hr the reaction mixture was brought to room temperature and dissolved in water and saturated with sodium chloride and extracted with diethylether several times. The ether extract was washed with saturated potassium carbonate solution, water and brine and dried over anhydrous sodium sulphate. The removal of the solvent furnished the phthalimide derivatives **(27a or 27b)** as a thick oil.

(S) 2-(1-hydroxybutyl) phthalimide (24a)



Yield : 93%.

$[\alpha]_D^{20}$: -11.0° (*c* 1.0 in MeOH).

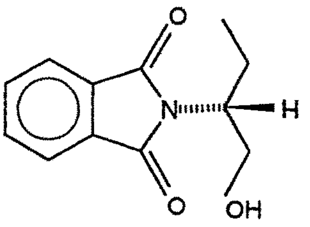
CHN found (calculated): C - 65.89 (65.75), H - 5.74 (5.93), N - 6.50 (6.39).

ν_{max} (Neat)/cm^{-1} : 3500, 2950, 1710, 1610, 1470, 1370, 1230.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.90 (2H,m,-CH_2), 3.80 (3H,m,-CH-CH_2-O), 5.30 (1H,s,-OH), 7.50 (4H, s,-C_6H_4).

m/z : 219 (M^+), 187, 159, 147, 129, 103, 76,and 50.

(R) 2-(1-hydroxybutyl) phthalimide (24b)



Yield : 93%.

$[\alpha]_D^{20}$: 21.0° (*c* 1.0 in MeOH)

CHN found (calculated): C - 65.70 (65.75), H - 5.89 (5.93), N - 6.30 (6.39).

ν_{max} (Neat)/cm^{-1} : 3500, 2950, 1700, 1610, 1470, 1360, 1230.

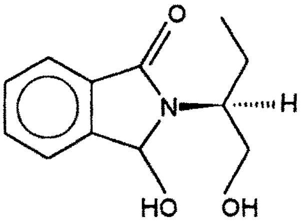
δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.90 (2H,m,-CH_2), 3.90 (3H,m,-CH-CH_2-O), 5.30 (1H,s,-OH), 7.50 (4H,s,-C_6H_4).

4.2.3.2 3-hydroxy-2-(1-hydroxy butyl) isoindolin-1-one (25a & 25b)

24a or **24b** (0.01 mole) was dissolved in 50ml of methanol or methanolic HCl (IN) in an R.B. flask equipped with a gas trap. The reaction mixture was cooled in an ice-salt bath. Sodium borohydride was added pinchwise and stirred continuously, till the reduction is complete, which was monitored by TLC.

After the completion of the reaction, water (5 ml) was added and the solvent was removed under reduced pressure. The residue was extracted with dichloro methane. The dichloro methane extract was dried over anhydrous sodium sulphate. Removal of the solvent furnished the hydroxy derivatives of phthalimides **(25a or 25b)**.

(S) 3-hydroxy-2-(1-hydroxybutyl) isoindolin-1-one (25a)



Yield : 90%.

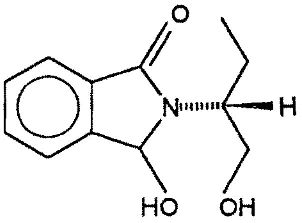
$[\alpha]_D^{20}$: 7.0° (*c* 1.0 in MeOH).

CHN found (calculated) : C - 65.26 (65.15), H - 6.91 (6.78), N - 6.49 (6.33).

ν_{max} (Neat)/cm^{-1} : 3450, 2950, 1680, 1610, 1460, 1360, 1240.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.70 (2H,m,-CH_2), 3.50-4.20 (3H,m,-CH-CH_2-O), 5.20 (2H,s,2-OH), 5.80 (1H,d,-CH on the 5 membered ring), 7.40 (4H, m,-C_6H_4).

(R) 3-hydroxy-2(1-hydroxybutyl) isoindolin-1-one (25b)



Yield : 90%.

$[\alpha]_D^{20}$: 25° (*c* 1.0 in MeOH)

CHN found (calculated) : C - 65.37 (65.15), H - 6.49 (6.78), N - 6.44 (6.33).

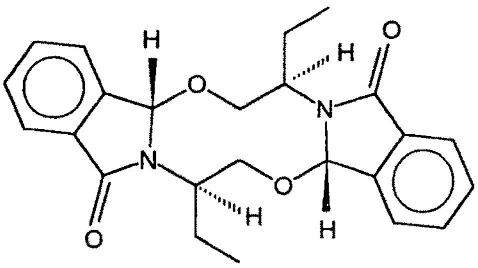
ν_{max} (Neat)/cm^{-1} : 3500, 2950, 1680, 1470, 1360, 1220.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.70 (2H,m;-CH_2), 4.20 (3H,m,-CH-CH_2-O), 5.20 (2H,s,2-OH), 5.70 (1H,D,-CH on the 5 membered ring), 7.50 (4H, m,-C_6H_4).

4.2.3.3 Formation of the chiral ten membered fused ring system 27a & 27b

Trifluoro acetic acid (0.02 moles) was dissolved in dichloromethane (10ml) in a two necked R.B. flask. The reaction mixture was bubbled with nitrogen. A solution of **22a** or **22b** (0.01 mole) was dissolved in CH_2Cl_2 (10ml) and added to the above solution by means of a pressure equalising funnel, over half an hour. The reaction mixture was stirred at room temperature for 16 hrs in N_2 atmosphere. The reaction mixture was neutralised with Na_2CO_3 solution. The organic layer was separated and dried over anhyd. Na_2SO_4. The organic layer on evaporation furnished a residue which was chromatographed on a silica gel column using petroleum ether (60-80°C) - ethylacetate, furnished the cyclised ten membered ring products **27a** and **27b**.

The chiral ten membered fused ring system (27a)



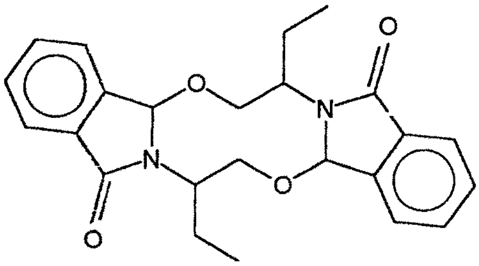
Yield	: 40%.
$[\alpha]_D^{20}$	:14.0° (*c* 0.5 in $CHCl_3$)
CHN found (calculated)	: C- 70.76 (70.93), H- 6.52 (6.40), N- 6.93 (6.89)
ν_{max} (KBr)/cm^{-1}	: 2950, 1700, 1510, 1470, 1360.
δ ppm ($CDCl_3$)	: 0.90 (6H,t,2-CH_3), 1.80 (4H,m,2-CH_2), 3.50 (4H,t,2-CH_2-O), 4.20 (2H,s,2-CH) 6.00 (2H,s,2-CH on the 5 membered ring), 7.70 (8H,m,2-C_6H_4).

Crystal data and Structure refinement

Crystal data of 27a : $C_{24}H_{26}N_2O_4$, Mw - 406.47., Orthorhombic, $P2_12_12_1$, a= 9.747 (1), b= 9.824 (1), c= 21.978 (2) A°, V= 2104.5 (4) A^{o3}, z= 4, D_c= 1.283 gm cm^{-3} F(000) =864, Mo-K_α radiation λ = 0.71073 A°, 4154 reflection were collected in the range 4.5 < 2θ < 50°, h 0 to 11, k 0 to 11 , l= -26 to -26: 3701 independent (R merging = 0.0128), 3192 observed [I > 2σ (I)]. The structure was solved by SIR 92(9) and refined by SHELX93(10). Anisotropic displacement parameters were used for nonhydrogen atoms. The hydrogen atoms were located by difference fourier map and refined isotropically. Final R= 0.0266, Rw (0n F^2) = 0.0604 [with $w^{-1} = \sigma^2 (Fo^2) + (0.03666p)^2$, where p= ($Fo^2$ + $2Fo^2$)/3.

The absolute configuration of **27a** was found to be ***(2S*, 11R*, 14S*, 23R*)***, which was assigned according to the chirality of carbon atom C-11 and C-23, known from the reagent, which is determined by single crystal X-ray diffraction. List of fractional atomic co-ordinates, atomic diaplacement parameters, Bond lengths and angles are also presented (Tables IV.II.I - IV.II.IV).

The chiral ten membered fused ring system (27b)



Yield	: 40%.
$[\alpha]_D^{20}$	: 134.0° (*c* 0.5 in $CHCl_3$)
CHN found (calculated)	: C - 70.01 (70.93), H - 6.46 (6.40), N - 6.74 (6.89).
ν_{max} (KBr)/cm^{-1}	: 2950, 1710, 1510, 1470, 1350.
δ ppm ($CDCl_3$)	: 0.90 (6H,m,-2-CH_3), 1.70 (4H,m,2-CH_2), 3.60 (4H,m,2-CH_2-O), 4.50 (2H,m,2-CH) 6.00 (2H,d,2-CH on the 5 membered ring), 7.80 (8H, m, 2-C_6H_4).

TABLE IV.II.I :

Final Coordinates and equivalent or Isotropic displacement parameters for 27a

	x	y	z	Ueq/iso
O1	0.09168(10)	0.23999(10)	0.19884(4)	0.0365(2)
C2	0.18344(15)	0.1821(12)	0.155880(6)	0.0350(3)
C3	0.1846(2)	0.26110(15)	0.09698(6)	0.0385(3)
C4	0.0770(2)	0.2875(2)	0.05745(7)	0.0502(4)
C5	0.1052(2)	0.3664(2)	0.00653(3)	0.0641(5)
C6	0.2359(3)	0.4178(2)	-0.00410(8)	0.0647(6)
C7	0.3413(2)	0.3931(2)	0.03599(8)	0.0531(5)
C8	0.3137(2)	0.3137(2)	0.08684(6)	0.0403(4)
C9	0.4039(2)	0.27336(15)	0.13782(7)	0.0403(4)
N10	0.32472(12)	0.19865(12)	0.17692(5)	0.0360(3)
C11	0.3849(2)	0.1196(2)	0.22707(7)	0.0371(3)
C12	0.3017(2)	0.1273(2)	0.28512(7)	0.0376(3)
O13	0.18883(10)	0.03364(9)	0.28170(4)	0.0353(2)
C14	0.08684(15)	0.05130(15)	0.32690(7)	0.0338(3)
C15	0.14124(15)	0.06841(15)	0.39083(6)	0.0362(4)
C16	0.2288(2)	-0.0145(2)	0.42387(8)	0.0500(4)
C17	0.2623(2)	0.0260(2)	0.48232(9)	0.0631(5)
C18	0.2116(2)	0.1449(2)	0.50722(8)	0.0660(5)
C19	0.1254(2)	0.2281(2)	0.47392(8)	0.0557(5)
C20	0.0926(2)	0.1881(2)	0.41518(6)	0.0394(3)
C21	0.0058(2)	0.2571(2)	0.3692(6)	0.0381(3)
N22	0.00590(11)	0.17540(12)	0.31879(5)	0.0336(3)
C23	-0.09309(15)	0.1947(2)	0.26908(7)	0.0391(3)
C24	-0.0302(2)	0.1624(2)	0.20774(7)	0.0410(4)
O25	0.52589(11)	0.29928(13)	0.14496(5)	0.0558(3)
C26	0.4159(2)	-0.0268(2)	0.20835(8)	0.0483(4)
C27	0.5107(2)	-0.0409(2)	0.15398(9)	0.0579(5)

	x	y	z	Ueq/iso
O28	-0.05667(12)	0.36438(12)	0.37458(5)	0.548(3)
C29	-0.2214(2)	0.1079(2)	0.27754(9)	0.0521(4)
C30	-0.2916(2)	0.1230(2)	0.33821(10)	0.0596(5)
H2	0.1646(14)	0.0867(15)	0.1503(6)	0.028(4)
H4	-0.147(18)	0.2485(20)	0.0653(7)	0.060(5)
H5	0.0321(21)	0.3852(20)	-0.0230(9)	0.070(6)
H6	0.0540(22)	0.4693(21)	0.0394(9)	0.073(6)
H7	0.4343(21)	0.4260(18)	0.0303(8)	0.062(6)
H11	0.4723(15)	0.1665(15)	0.2343(6)	0.037(4)
H12A	0.3631(15)	0.1016(15)	0.3205(7)	0.036(4)
H12B	0.2702(14)	0.2202(16)	0.2926(6)	0.032(4)
H14	0.0309(14)	-0.0273(15)	0.3233(6)	0.031(4)
H16	0.2586(19)	-0.0999(18)	0.4056(8)	0.060(5)
H17	0.3226(22)	-0.0291(21)	0.5063(9)	0.073(6)
H18	0.2297(20)	0.1698(19)	0.5497(9)	0.077(6)
H19	0.0838(20)	0.3112(21)	0.4917(9)	0.071(6)
H23	-0.1188(14)	0.2893(16)	0.2705(6)	0.037(4)
H24A	-0.0099(16)	0.0644(16)	0.2051(7)	0.042(4)
H24B	-0.0968(15)	0.1869(16)	0.1753(7)	0.041(4)
H26A	0.3337(20)	-0.0733(18)	0.2003(7)	0.057(5)
H26B	0.4597(19)	-0.0740(19)	0.2421(9)	0.066(6)
H27A	0.5280(19)	-0.1314(23)	0.1444(9)	0.070(6)
H27B	0.5989(23)	0.0111(22)	0.1589(9)	0.083(7)
H27C	0.4692(21)	-0.0032(21)	0.1164(9)	0.075(6)
H29A	-0.2846(20)	0.1349(19)	0.2446(8)	0.067(6)
H29B	-0.1959(19)	0.0097(21)	0.2719(8)	0.062(5)
H30A	-0.3771(21)	0.0701(19)	0.3406(8)	0.067(6)
H30B	-0.3126(19)	0.2204(23)	0.3481(8)	0.073(6)
H30C	-0.2332(21)	0.0913(19)	0.3717(9)	0.068(6)

TABLE IV.II.II

Anisotropic displacement parameters for 27a in the form :

$T = \exp[-2\pi^2 (U_{11}h2a^{*2} + 2U_{22}klb^{*}c^{*}]$

O1	0.0338(5)	0.0375(5)	0.0381(5)	-0.0023(4)	0.0025(4)	0.0007(5)
C2	0.0346(8)	0.0330(8)	0.0374(8)	-0.0041(6)	-0.0011(7)	0.0002(7)
C3	0.0458(9)	0.0360(8)	0.0388(7)	-0.0066(6)	0.0011(7)	0.0035(7)
C4	0.0527(10)	0.0585(11)	0.0393(9)	-0.0035(8)	0.0053(8)	0.0032(9)
C5	0.0751(14)	0.0749(13)	0.0421(10)	0.0049(9)	-0.0102(10)	0.0107(12)
C6	0.090(2)	0.0641(12)	0.0399(10)	0.0115(9)	0.0034(11)	0.0040(12)
C7	0.0651(12)	0.503(10)	0.0439(10)	0.0036(8)	0.0085(9)	-0.0014(9)
C8	0.0491(9)	0.0353(8)	0.0364(8)	-0.0032(7)	0.0040(7)	0.0011(7)
C9	0.0407(9)	0.0366(8)	0.0437(8)	-0.0011(7)	0.0063(7)	-0.0033(7)
N10	0.0319(6)	0.0383(7)	0.0377(6)	0.0030(5)	-0.0010(5)	-0.0010(6)
C11	0.0283(8)	0.0444(8)	0.0385(8)	0.0025(7)	-0.0025(7)	0.0000(7)
C12	0.0325(8)	0.0411(8)	0.0391(9)	-0.0030(7)	-0.0025(7)	-0.0020(7)
O13	0.0316(5)	0.0352(5)	0.0390(5)	-0.0034(4)	0.0018(5)	0.0001(5)
C14	0.0302(7)	0.0313(7)	0.0399(8)	0.0009(6)	0.0034(7)	0.0002(7)
C15	0.0323(8)	0.0390(8)	0.0372(8)	0.0068(7)	0.0040(6)	-0.0006(7)
C16	0.0428(10)	0.0563(11)	0.0508(10)	0.0122(9)	0.0070(8)	0.0103(8)
C17	0.0530(11)	0.091(2)	0.0456(10)	0.0215(11)	-0.0018(9)	0.0119(11)
C18	0.067(12)	0.0926(15)	0.0383(10)	0.0014(10)	-0.0090(9)	-0.0022(13)
C19	0.0656(11)	0.0590(11)	0.0426(9)	-0.0083(9)	-0.0015(9)	-0.0008(10)
C20	0.0401(8)	0.0411(8)	0.0369(8)	0.0008(7)	0.0033(7)	-0.0007(7)
C21	0.0410(8)	0.0321(8)	0.0414(8)	0.0009(7)	0.0072(7)	0.0020(7)
N22	0.0308(6)	0.0338(6)	0.0363(6)	-0.0003(5)	-0.0007(5)	0.0032(5)
C23	0.0305(7)	0.0432(9)	0.0435(8)	0.0022(7)	-0.0017(7)	0.0050(7)
C24	0.0312(8)	0.0514(10)	0.0404(9)	-0.0005(7)	-0.0059(7)	-0.0011(7)
O25	0.0415(7)	0.0673(8)	0.0586(7)	0.0086(6)	0.0022(5)	-0.0148(6)
C26	0.0490(10)	0.0454(9)	0.0503(10)	0.0074(8)	0.0066(9)	0.0106(9)
C27	0.0580(12)	0.0574(12)	0.0583(12)	-0.0079(10)	0.0150(10)	0.0062(11)
O28	0.0719(8)	0.0389(6)	0.0537(7)	-0.0021(5)	0.0085(6)	0.0177(6)
C29	0.0320(8)	0.0636(12)	0.0607(11)	0.0053(10)	-0.0023(8)	-0.0028(9)
C30	0.0480(11)	0.0596(13)	0.0712(14)	0.0191(11)	0.0135(10)	-0.0037(10)

TABLE IV.II.III :

Bond distances (A^0) for 27a

O1-C2	1.421(2)	O13-C14	1.416(2)
O1-C24	1.425(2)	C12-O13	1.436(2)
C1-N10	1.462(2)	C14-N22	1.463(2)
C9-N10	1.368(2)	C21-N22	1.369(2)
N10-C11	1.470(2)	N22-C23	1.470(2)
C2-C3	1.508(2)	C14-C15	1.511(2)
C3-C8	1.379(2)	C15-C20	1.376(2)
C3-C4	1.380(2)	C15-C16	1.385(2)
C4-C5	1.387(3)	C16-C17	1.384(3)
C5-C6	1.390(3)	C17-C18	1.382(3)
C6-C7	1.376(3)	C18-C19	1.381(3)
C7-C8	1.389(2)	C19-C20	1.387(2)
C9-O25	1.226(2)	C21-O28	1.223(2)
C11-C26	1.526(2)	C23-C29	1.525(2)
C26-C27	1.517(2)	C29-C30	1.506(3)
C2-H2	0.962(14)	C14-H14	0.948(15)
C4-H4	1.00(2)	C14-H16	0.97(2)
C5-H5	0.98(2)	C17-H17	0.96(2)
C6-H6	0.94(2)	C18-H18	0.98(2)
C7-H7	0.97(2)	C19-H19	0.99(2)
C11-H11	0.981(15)	C23-H23	0.963(15)
C12-H12A	1.014(15)	C24-H24A	0.98(2)
C12-H12B	0.977(15)	C24-H24B	0.99(2)
C26-H26A	0.094(2)	C29-H29A	0.99(2)
C26-H26B	0.97(2)	C29-H29B	1.00(2)
C27-H27A	0.93(2)	C30-H30A	0.98(2)
C27-H27B	1.01(2)	C30-H30B	1.00(2)
C27-H27C	0.99(2)	C30-H30C	0.98(2)

TABLE IV.II.IV :

Bond Angles (⁰) for 27a

C2-O1-C24	113.70(11)	C14-O13-C12	115.01(10)
O1-C2-N10	109.69(11)	O13-C14-N22	113.27(11)
O1-C2-C3	111.68(12)	O13-C14-C15	114.81(12)
N10-C2-C3	02.00(12)	N22-C14-C15	102.11(11)
C8-C3-C4	121.04(14)	C20-C15-C16	120.72(15)
C8-C3-C2	109.78(13)	C20-C15-C14	109.62(12)
C4-C3-C2	129.13(15)	C16-C15-C14	129.65(15)
C3-C4-C5	117.9(2)	C17-C16-C15	117.6(2)
C4-C5-C6	121.0(2)	C18-C17-C16	121.7(2)
C7-C6-C5	120.9(2)	C19-C18-C17	120.5(2)
C6-C7-C8	118.0(2)	C18-C19-C20	117.8(2)
C3-C8-C7	121.2(2)	C15-C20-C19	121.6(2)
C3-C8-C9	108.64(12)	C15-C20-C21	108.84(12)
C7-C8-C9	130.2(2)	C19-C20-C21	129.5(2)
O25-C9-N10	125.31(15)	O28-C21-N22	125.67(14)
O25-C9-C8	128.16(14)	O28-C21-C20	127.87(14)
N10-C9-C8	106.53(12)	N22-C21-C20	106.45(12)
C9-N10-C2	113.04(12)	C21-N22-C14	112.97(11)
C9-N10-C11	121.94(12)	C21-N22-C23	121.73(12)
C2-N10-C11	123.71(12)	C14-N22-C23	123.50(12)
N10-C11-C12	113.07(12)	N22-C23-C24	111.66(12)
N10-C11-C26	111.99(13)	N22-C23-C29	112.07(13)
O13-C12-C11	109.55(12)	O1-C24-C23	110.32(12)
C27-C26-C11	114.81(15)	C30-C29-C23	115.2(2)
O1-C2-H2	110.7(8)	O13-C14-H14	104.2(8)
N10-C2-H2	109.1(8)	N22-C14-H14	111.0(8)
C3-C2-H2	113.3(8)	C15-C14-H14	111.7(8)
C3-C4-H4	120.1(10)	C17-C16-H16	124.0(10)

C5-C4-H4	122.0(10)	C15-C16-H16	118.3(11)
C4-C5-H5	119.9(11)	C18-C17-H17	118.6(12)
C6-C5-H5	119.1(11)	C16-C17-H17	119.6(12)
C7-C6-H6	118.8(13)	C19-C18-H18	117.8(12)
C5-C6-H6	120.3(13)	C17-C18-H18	121.5(12)
C6-C7-H7	123.8(10)	C20-C19-H19	120.3(11)
C18-C19-H19	121.8(11)	C8-C7-H7	118.2(11)
N10-C11-H11	102.7(8)	N22-C23-H23	105.7(9)
C12-C11-H11	107.7(8)	C24-C23-H23	109.7(9)
C26-C11-H11	108.3(8)	C29-C23-H23	108.8(9)
O13-C12-H12A	109.4(8)	O1-C24-H24A	110.3(9)
C11-C12-H12A	108.6(8)	C23-C24-H24A	109.8(9)
O13-C12-H12B	111.5(8)	O1-C24-H24B	108.6(8)
C11-C12-H12B	110.9(8)	C23-C24-H24B	108.7(8)
C27-C26-H26A	109.0(10)	C30-C29-H29A	109.9(11)
C11-C26-H26A	109.9(11)	C23-C29-H29A	105.8(11)
C27-C26-H26B	106.9(11)	C30-C29-H29B	108.4(11)
C11-C26-H26B	109.3(11)	C23-C29-H29B	108.6(11)
C26-C27-H27A	112.2(12)	C29-C30-H30A	112.3(11)
C26-C27-H27B	112.9(12)	C29-C30-H30B	112.3(11)
C26-C27-H2C	111.9(12)	C29-C30-H30C	111.7(11)
H12A-C12-H12B	106.8(11)	H24A-C24-H24B	109.1(12)
H26A-C26-H26B	106.6(15)	H29A-C29-H29B	108.8(15)
H27A-C27-H27B	110.8(17)	H30A-C30-H30B	108.6(15)
H27A-C27-H27C	104.0(17)	H30A-C30-H30C	106.5(15)
H27B-C27-H27C	104.4(16)	H30B-C30-H30C	105.0(16)

4.2.4 REFERENCES

1. Meyers A I, Lefker B A, Wanner K T, & Aitken R A, *J.Org.Chem.*, 51 (1986) 1936.
2. Meyers A.I & Lefker B A, ***J. Org. Chem.***, **51** (1986) 1541.
3. Meyers A I & Flemming S A, ***J. Am. Chem. Soc.***, **108** (1986) 306.
4. Meyers A I & Lefker B.A, ***Tetrahedron.***, **43** (1987) 5663.
5. Meyers A I, Harre M & Garland R, ***J. Am. Chem. Soc.***, **106** (1984) 1146.
6. Meyers A I, Lefker B A, Sowin J J & Westrum L J, ***J. Org. Chem.***, **54** (1989) 4243.
7. Hadfield P S, Galf R H B, Sawyer Y Layland N J, Page M I, ***J. Chem. Soc. Perkin Trans I.***, (1997) 503.
8. Personnel Communication with Steven M.Allin, Loughborough University, U.K.
9. Altomare A, Cascarano G, Giacovazzo G, Guagliardia A, Burla M C, Polidori G & Camalli M., ***J. Appl. Cryst.***, **27** (1994) 435.
10. Sheldrick G M, 1993, Programme for the refinement of crystal structure, University of Goettingen, Germany.