PMR CHARACTERIZATION OF DIASTEREOMERIC FORMS OF ACYCLIC COMPOUNDS BEARING TWO EQUIVALENT CHIRAL ATOMS IN 1,5-POSITIONS

D. GIARDINA', R. BALLINI, G. M. CINGOLANI and B. R. PIETRONI Istituto di Chimica Organica e Farmaceutica dell'Universita', Camerino, Italy

and

. A. CAROTTI and G. CASINI* Istituto di Chimica Farmaceutica e Tossicologica dell'Universita', Via Amendola 173, 70126 Bari, Italy

(Received in UK 30 May 1978; Accepted for publication 8 August 1978)

Abstract—Assignment of configurations to diastereomeric pairs was based on anisochronism of diastereotopic protons of suitable *probe* groups, at various distances from both chiral centers.

PMR differentiation and identification of *meso* and *dl* forms of acyclic structures with two equivalent chiral atoms have been widely studied when the asymmetric centers were separated by one atom.¹ The very strict approach was based on symmetry principles² such as anisochronism of diastereotopic groups in the *meso* form.

The same criterion was also applied to some cases of molecules having asymmetric center separated by two C atoms³⁻⁵ whereas most of the works on structures with longer atom chain separation made use of an empirical criterion, i.e. differences in chemical shifts, that were not predictable *a priori.*⁶⁻¹⁰

It is known that the mediated effect of an asymmetric center on the anisochronism of diastereotopic groups decreases with increasing distance;¹¹ factors affecting conformational equilibrium in solution, such as temperature,¹² or nature of solvent,¹¹ however, can influence the critical chain length at which anisochronism disappears at a given PMR frequency.

The present work is an attempt to show the effect of distance from two equivalent chiral atoms on anisochronism of diastereotopic groups. Thus, a series of compounds was prepared, with two asymmetric centers separated by three C atoms and bearing two equal *probe* groups joined to the central atom, to provide readily analyzable first-order signal systems. Schemes A, B, C show the synthetic routes by which the three fundamental structures 1, 2 and 3 were obtained. *Probe* groups

were geminal Me groups in 1a and 1b (four bond separation of probe protons from both chiral centers), geminal carbomethoxy groups in 3 (two more bond separation), geminal methylene groups in 2, with additional Me (acetic) groups in 2b and 2c, thus providing *probe* protons with a seven bond separation from the asymmetric atoms.

RESULTS AND DISCUSSION

As shown in Table 1, differentiation of diastereomers was always possible and the assignment of configurations was achieved for all structures on the basis of anisochronism of diastereotopic *probe* protons. Me *probe* groups are diastereotopic and therefore anisochronous in *meso* forms and are equivalent and isochronous in *dl* forms (2).

In methylene probe groups, which miss the threefold axis of symmetry present in Me groups, probe protons should always be diastereotopic in pairs (Fig. 1): in meso form geminal protons of each methylene group are enantiotopic and isochronous, whereas the two methylene groups are diastereotopic each other and therefore anisochronous (predicted signal: two singlets); in *dl* form geminal protons of each methylene group are diastereotopic and hence anisochronous, being equivalent in pairs to those of the other methylene group (predicted signal: AB system).

Only in compound 2c, the meso form showed no anisochronism in either probe group pairs; however the



meso,(RS form):point group Cs



dl,(RR form): point group C₂

Fig. 1. Symmetry relationship between CH₂ probe protons in 2a (W = -OH), 2b and 2c (W = -OAc). G_R and G_S refer to the two opposite configurations of chiral centers. The proton pairs H_A-H_A , and H_B-H_B , are enantiotopic in RS form and equivalent in RR (SS) form.

							, [
Compounds	N	Probe groups	Biastereomerie form	Diastercomeric purity	V, Probe -CH ₃ singlet(s)	V. Probe -CH ₂		Branch - CH ₂ -CH-Z, AB	chain X system		V, uther protons	
				(⁶ ¹)		AB System	я ,	V, V _R V _X	JAR JAY	J _{BY}		
1 10	1 07	-011	meso	001 ~	1.06 0.91		i.	1.61 1.83 4.79	15 8.5	3.5	2.1818,24,041	
		~	व	0 01 ≈	1.02 1.02			1.34 2.21 4.71	15 10	2	L.17(s,2H,0H)	
۹ ۲	-0000H3	-013	nteso	001 ≂	0.98 0.94		1	1.65 2.01 5.85	15 9.5		.89	
			1 I	ح 100	0, 46 0, 96		1	1.62 2.00 5.82	8 17	÷	$(98) \left(\begin{array}{c} 5, 00, \\ -0.000 \end{array} \right)_{3}$	
S	-01	10 E) -	likeso	99	1	3.68 3.47	1	1.76 1.84 1.86	15 3	x	011 protons	
		21	÷.	26	:	3.60 3.60	¢~-	1.84 1.88 4.85	15 10	2	exchanged	

Table 1. PMR data of structure C₆H₅-CHZ-CH₂-CY₂-CH₂-CHZ-C₆H₅

5 1.93 s.611, benzylic	+ 2.00 - 000H3	··-	2		
.5 3	6	1 5 5	2	2	ъ Э
-	5	5 8			ę
1.85 2.19 5.91	1.81 2.19 5.84	2.41 2.49 4.97 1	2.49 2.49 5.06 ?	3.04 3.04 1.94 ?	3.003.12 1.97
;	11.5	}	12		1
3.95	3.88	3.72	3.48	1	1
3,99	4.04	3.72	3.75		ł
2.01	2.03	1.95	1.94	3.22	3.34
2.04	2.03	1.95	1:6 - 1	3.54	3, 34
80	92	80	76	86	9.5
0.000	Ŧ	<u>II (530</u>	ᆌ	IIESO	<u>úl</u>
- CH ₂ 0C0CH ₃		- CH 2 00000H 3		-000013	
-000H3		: #		- 13 r.	
ลึ		ک د		e	

*Chemical shifts (v) are expressed in 8 (ppm) and coupling constants in Hertz. All spectra were recorded a 100 MHz in CDCl₃ using TMS as internal standard; only for 2a (sparingly soluble in CDCl₃)CD₅OD was utilized. Disastereomeric purity was calculated from intensity ratio of *probe* signals. Effect of temperature or solvent changes on degenerated signals were investigated only for *dl* 2a, and no significant variation of the spectra was observed.

** Aromatic proton signals are not listed; they gave singlets or multiplets from 7.4 to 7.1ô.

٦



PMR signal of methylene probe groups, which appeared as an AB system in dl form made assignment possible also for 2c structure. The same behaviour of methylene probe groups was observed in dl 2b, but not in dl 2a where the expected AB system degenerated to a singlet. Fortuitous compensation of the mediated magnetic influence of the two chiral centers for a particular distribution of conformational populations might account for this degeneration and, possibly, also for that observed in *meso* 2c.

Differences between diastereomers were also observed in the ABX systems of chain branches (Table 1); degeneration to an A_2X system was observed in only one diastereomer of 2c and 3, regardless of their configurations.

In conclusion, our results show that in one case at least (*meso* 2b) probe protons separated from the chiral centers by seven bonds can still show anisochronism at 100 MHz.

EXPERIMENTAL

General. M.ps were determined on a Büchi apparatus and are uncorrected. M.ps of diastereomers 1, 2 and 3 referred to diastereomeric purity reported in Table 1. Elemental analyses were made by dr. R. De Leonardis, using a Hewlett-Packard 185 C, H, N analyzer.

NMR spectra were recorded on a Varian HA 100 or a Jeol C-60 HL spectrometer, using TMS as internal standard. Chemical shifts are reported in ppm (δ) and the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet. NMR data of diastereomeric forms are listed in Table 1 and and are not reported in this section. Column chromatographies were performed with Merck silica gel (230-400 mesh ASTM).

In the fractional crystallization of diastereomeric mixtures, the *dl* form always crystallized first.

Acetylation of separated diastereomeric forms 1a and 2a and diol 8 was carried out in pyridine and Ac_2O by the usual procedure.

1,5-Diphenyl-3,3-dimethyl-pentane 1,5-diol (1a). A mixture of 4^{13} (0.6 g, 2.14 mmol) and NaBH₄ (0.057 g, 1.51 mmol) in abs EtOH (30 ml) was heated at 50-60° for 24 hr. After removing the solvent *in vacuo*, the residue was dissolved in water and the soln extracted with ether. The separated organic layer was dried on Na₂SO₄, filtered, and evaporated to dryness to give a diastereomeric mixture of diols Ia (0.59 g, 97% yield). Separation of diastereomers was obtained by column chromatography using 80:20 hexane-EtOAc as eluant. Crystallization of both forms from petrol ether gave: *meso* form, m.p. 84-86°, (Found: C, 80.03; H, 8.63. C₁₉H₂₄O₂ (284.4) requires: C, 80.24; H, 8.51%); *dl* form, m.p. 109-111°, (Found: C, 80.15; H, 8.34. required: as above).

1,5-Diphenyl-1,5-diacetoxy-3,3-dimethyl-pentane (1b). Meso 1b was crystallized from hexane, m.p. 64-66° (86% yield). (Found: C, 74.98; H, 7.80. $C_{23}H_{28}O_4$ (368.5) requires: C, 74.97; H, 7.66%). Efforts to crystallize the dl form, were unsuccessful, (Found: C, 75. 25; H, 7.95. required: as above).

1,5-Diphenyl-3,3-bis-(methoxycarbonyl)-pentane 1,5-dione (5). Dimethyl malonate (1.1 g, 8.3 mmol) and finely powdered Na (0.41 g, 18 mmol) were refluxed in dry benzene (100 ml) and stirred mechanically for 2 days. Next, a soln of phenacyl bromide (4 g, 20 mmol) in dry benzene (10 ml) was added dropwise. The mixture was refluxed for another day, cooled, washed with water, and dried on Na₂SO₄. After filtration, the solvent was removed *in vacuo* and the remaining crude product was crystallized from MeOH to give 5 (1.5 g, 49% yield) m.p. 146–148°. (Found: C, 68.17; H, 5.20. C₂₁H₂₀O₆ (368.4) requires: C, 68.47; H, 5.47%). NMR (CDCl₃/60MHz) & 3.80 (s, 6H, -CH₃); 4.08 (s, 4H, -CH₂); 7.30–7.80 (m, 6H) and 7.90–8.40 (m, 4H) (arom).

1,5-Diphenyl-3,3-bis-(hydroxymethyl)-pentane 1,5-diol (2a). A soln of 5 (1 g, 2.7 mmol) in abs ether (30 ml) was added dropwise to a suspension of LAH (1.67 g, 44 mmol) in abs ether (40 ml) and was then refluxed for 1 hr and stirred at room temp during 24 hr. Ice-water was carefully added to the cooled mixture to remove excess LAH.

After adding 10% H_2SO_4 (30 ml), the organic layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were washed with saturated brine, water, and dried on Na₂SO₄. Filtration and evaporation of the solvent gave 0.75 g of reduction products. Column chromatography using 50:50 cyclohexane-EtOAc as etuant, gave triol 6 as first fraction (0.08 g), m.p. 110-112° from CHCl₃. (Found: C, 75.81; H, 7.86. C₁₉H₂₄O₃ (300.4) requires: C, 75.97; H, 8.05%);

MR (CD₃OD)
$$\delta$$
: 1.55–1.90 (m, 4H. CH₂–CH₂–CH₂–CH₂–CH);

1

2.40-2.70 (m, 2H, Ph-CH₂); 3.48 (s, 2H, CH₂-O); 3.62 (s, 2H, CH₂-O); 4.78-4.94 (m, 1H, CH-); 7.00-7.42 (m, 10 H, arom) and a mixture of diastereoisomers 2a as second fraction (0.55 g, 68% yield). The latter was separated by fractional crystallization with ether to give: *meso* form, m.p. 132-134°, (Found: C, 72.24; H, 7.70, C₁₉H₂₄O₄ (316.4) requires: C, 72.12; H, 7.65%); *dl* form, m.p. 140-142°, (Found: C, 72.30; H, 7.48; required: as above).

Reduction of 5, using various amounts of NaBH₄, always gave complex mixtures, containing 2a and partial reduction products with IR lactone CO absorption.

1,5 - Diphenyl - 1, 5 - diacetoxy - 3, 3 - bis - (acetoxymethyl) - pentane (2b). Meso 2b was obtained in 82% yield, m.p. 80-83° from hexane (Found: C, 66.76; H, 6.62. $C_{27}H_{32}O_8$ (484.5) requires: C, 66.92; H, 6.66%), dl 2b was prepared in 84% yield, m.p. 89-92° from hexane (Found: C, 67.13; H, 6.62. required: as above).

1,5-Diphenyl-3,3-bis-(methoxycarbonyl)-pentane (7). A mixture of dimethyl malonate (1 g, 7.6 mmol) and finely powdered Na (0.39 g, 17 mmol) was refluxed in dry toluene (40 ml), and stirred mechanically for 1 day. Then, a soln of phenethyl bromide (2.8 g, 15.2 mmol) in dry toluene (5 ml) was added dropwise and the mixture was refluxed during 2 days. After cooling, the solvent was removed *in vacuo* and water was carefully added to the residue. The aqueous soln was extracted with ether and the crude product obtained after drying ethereal extracts on Na₂SO₄ and removing the solvent, was crystallized from MeOH to give 7 (1.7 g, 66% yield), m.p. 76-78° (Found: C, 74.04; H, 7.21. C₂₁H₂₄O₄ (340.4) requires: C, 74.09; H, 7.11%); NMR (CDCl₃/60 MHz) 8: 2.25-3.40 (m, 8H, -CH₂); 4.14 (s, 6H, -CH₃); 7.60 (s, 10 H, arom).

1,5 - Diphenyl - 3,3 - bis - (hydroxymethyl) - pentane (8). A

soln of 7 (1.5 g, 4.4 mmol) in abs ether (20 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (0.20 g, 5.3 mmol) in abs ether (40 ml). After stirring at room temp for 1 day, the mixture was refluxed for 1 hr, cooled and carefully added with ice-water. The organic layer was separated and the aqueous soln extracted with ether. The combined extracts were dried on Na₂SO₄ and evaporated under vacuum to give **8** (1.14 g, 91% yield), m.p. 144–146° from ether. (Found: C, 79.93; H, 8.53. C₁₉H₂₄O₂ (284.4) requires: C, 80.24; H, 8.51%); NMR (DMSOd₆/60 MHz) δ : 1.36–1.64 (m, 4H, Ph-CH₂-CH₂-); 2.46– 2.70 (m, 4H, Ph-CH₂, partially overlapped by solvent signal); 3.38 (d, 4H, -CH₂-O, J = 6 Hz); 4.36 (t, 2H, -OH, J = 6 Hz); 7.00-7.30 (m, 10 H, arom).

1,5-Diphenyl-3,3-bis-(acetoxymethyl)-pentane (9). Diacetate 9 was obtained in 71% yield m.p. 78-79° from MeOH-H₂O (Found: C, 74.82; H, 7.77. $C_{23}H_{28}O_4$ (368.5) requires: C, 74.97; H, 7.66%);

NMR (CDCl₃/60 MHz) δ : 1.50–1.92 (m, 4H, -CH₂-C-CH₂-O);

2.10 (s, 6H, $-CH_3$); 2.40–2.90 (m, 4H, PH- CH_2); 4.10 (s, 4H, $-CH_2$ -O); 7.30 (s, 10 H arom).

Bromination of 1,5-diphenyl-3,3-bis-(acetoxymethyl)-pentane (9) and 1,5-diphenyl-3,3-bis-(methoxycarbonyl)-pentane (7). A soln of 7 or 9 (4 mmol), N-bromosuccinimide (1.5 g, 8.5 mmol) and benzoyl peroxide (0.04 g) in dry CCl₄ (25 ml) was refluxed for 1 hr. After cooling, the succinimide was filtered off and the solvent removed in vacuo to give a mixture of 3 or 2c, yield 96% and 93% respectively. Fractional crystallization from ether gave pure diastereomeric forms of 3 or 2c. Compound 3, meso form, m.p. 114-115°. (Found: C, 50.91; H, 4.28. $C_{21}H_{22}Br_2O_4$ (498.2) requires: C, 50.63; H, 4.45%). 3, dl form, m.p. 140-142°. (Found: C, 50.80; H, 4.51 required as above). Compound 2c, meso form, m.p. 77-79°. (Found: C, 52.72; H, 4.98. $C_{23}H_{26}Br_2O_4$ (526.3) requires: C, 52.49; H, 4.98%). 2c, dl form, m.p. 120-121°. (Found: C, 52.68; H, 5.05 required as above).

Acknowledgements-This work was supported by CNR, Rome.

REFERENCES

- ¹A. Gaudemer, Stereochemistry, Fundamental and Methods (Edited by H. B. Kagan), Vol. 1, p. 73. Georg Thieme, Stuttgart (1977).
- ²K. Mislow, *Topics in Stereochemistry* (Edited by N. L. Allinger and E. L. Eliel), Vol. 1, p. 1. Wiley-Interscience, New York (1967).
- ³D. Jung and A. A. Bothner-By, J. Am. Chem. Soc. 86, 4025 (1964).
- ⁴F. Taddei, Boll. Sci. Fac. Chim. Ind. Bologna 26, 107 (1968).
- ⁵G. Casini, M. Ferappi, B. R. Pietroni, F. Taddei and L. Schenetti, *Tetrahedron* 28, 1497 (1972).
- ⁶J. P. Vigneron, M. Dhaenens and A. Horeau, *Ibid.* 29, 1055 (1973).
- ⁷E. Larsson, Org. Magn. Res. 6, 103 (1974).
- ⁸H. Neudeck and K. Schlögl, Monatsh. Chem. 106, 229 (1975).
- ⁹F. U. Flother, G. Kraus, A. Zchenicke, P. Kurzay, W. Sauer and F. J. Struber, *J. pr. Chem.* 318, 1031 (1976).
- ¹⁰G. A. Tolstikov, N. N. Novitskaya, R. G. Kantyukova, L. V. Spirikhin, V. A. Palyulin and N. S. Zefirov, *Zh. Org. Khim.* 13, 894 (1977).
- ¹¹G. M. Whitesides, D. Holtz and J. D. Roberts, J. Am. Chem. Soc. 86, 2628 (1964).
- ¹²H. S. Gutowsky, J. Chem. Phys. 36, 3353 (1962).
- ¹³H. Zimmerman and J. A. Pincock, J. Am. Chem. Soc. 95, 3246 (1973).