Chemistry of Heterocyclic Compounds, Vol.35, No. 4, 1999

REGIOSELECTIVITY IN THE REACTION OF PARAFORMALDEHYDE WITH (1*S*,2*S*)-2-ARYL(HETARYL)METHYLAMINO-1-(4-NITROPHENYL)-1,3-PROPANEDIOLS

J. Couquelet, M. Madesclaire, F. Leal, V. P. Zaitsev, and S. Kh. Sharipova

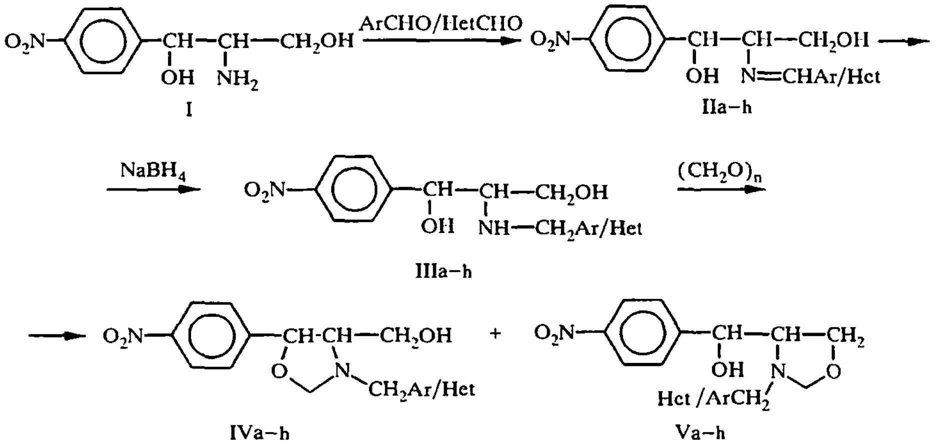
The reaction of paraformaldehyde with (1S,2S)-2-aryl(hetaryl)methylamino-1-(4-nitrophenyl)-1,3-propanediols produces a mixture of isomeric 3-aryl(hetaryl)methyl-4-hydroxymethyl-5-(4-nitrophenyl)- and 3-aryl(hetaryl)methyl-4-hydroxy(4-nitrophenyl)methyloxazolidines and is reversible.

The use of enantiomerically pure compounds as medicinal preparations, insecticidal formulations, and new materials shows promise [1, 2]. Therefore, the development of methods for the asymmetric synthesis of optically active compounds is a very interesting problem.

It is known that (+)-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (I), which is a side product in production of the antibiotic levomycetin, is widely used as a splitting agent, as various kinds of additives and as a material for nonlinear optics [2]. New biologically active compounds have been synthesized on its basis [2, 3]. We have described preparation of the corresponding Schiff bases [4, 5], 4-(4-nitrophenyl)-1-aza-3,7-dioxabicyclo[3.3.0]octane, and quaternary salts from the aminodiol I [6].

In the present work, I is reacted with several aromatic and heterocyclic aldehydes. Reduction of the resulting Schiff bases II by sodium borohydride and of the resulting substituted aminodiols III with paraformaldehyde produces the new oxazolidines IV (see Scheme 1 and Tables 1 and 2).

Scheme 1



Université d'Auvergne, Faculté de Farmacie, 28, Place Henri Dunant, Clermont-Ferrand, France; e-mail: michel.madesclaire@u-clermontl.fr; Samara State University, Samara 443011, Russia; e-mail: vzaitsev@ssu.samara.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 536-541, April, 1999. Original article submitted June 11, 1998; revision submitted November 19, 1998.

0009-3122/99/3504-0474$22.00©1999 KluwerAcademic/Plenum Publishers

TABLE 1. Characteristics of Compounds IV

Compound	Ar/Het	Empirical formula	Found, %			Calculated, %			Content of IV in reaction products,* %	mp, °C	[α], deg. (in acetone)	Yield*², %
			C	H	N	C	H	N				
IVa	Phenyl	$C_{17}H_{18}N_2O_4$	64,88	5,63	8,85	64,97	5,77	8,91	98	75...76	+19,6	90
IVb	3,4-Methylenedioxyphenyl	$C_{18}H_{18}N_2O_6$	60,17	4,97	7,91	60,34	5,06	7,82	100	115...116	-0,6	94
IVc	4-Methoxyphenyl	$C_{18}H_{20}N_2O_5$	62,93	5,76	8,01	62,79	5,85	8,14	88	65...66	+7,3	92
IVd	3,4-Dichlorophenyl	$C_{17}H_{16}Cl_2N_2O_4$	53,45	4,12	7,18	53,29	4,21	7,31	84	58...62	+13,2	88
IVe	3,4-Dimethoxyphenyl	$C_{19}H_{22}N_2O_6$	60,81	5,73	7,25	60,97	5,92	7,48	86	163...164	-3,3	86
IVf	2-Thienyl	$C_{15}H_{16}N_2O_4S$	56,41	5,13	8,63	56,25	5,04	8,74	88	84...85	+5,9	88
IVg	2-Furyl	$C_{15}H_{16}N_2O_5$	59,02	5,19	9,35	59,22	5,30	9,21	89	55...56	+34,6	90
IVh	2-Pyridyl	$C_{16}H_{17}N_3O_4$	60,76	5,56	13,18	60,95	5,44	13,33	87	liquid (tar)	+22,6	85

---

* According to PMR data.

*² Yields of mixtures of IV and V are given.

TABLE 2. PMR Spectral Characteristics for Substituted Oxazolidines IV

Compound	Chemical shifts, δ, ppm, SSCC (*J*), Hz							
	CHN, 1H, m	CH_2O	2H, m	CH_2Ar, 2H, q	OCH_2N, 2H, q	CHO, 1H, d	OH, 1H, t	Ar/Het
IVc	2,87...2,92	3,46...3,58	3,73 (*J* = 13,4)	4,54 (*J* = 6,1)	4,84 (*J* = 5,6)	4,97 (*J* = 5,6)	3,72 (3H, s, OCH_3) 6,84...7,17 (4H, q, *J* = 8,9, H_{Ar})	7,69...8,24 (*J* = 8,9)
IVd	2,90...2,95	3,52...3,63	3,85 (*J* = 14,0)	4,57 (*J* = 6,1)	4,84 (*J* = 4,6)	5,05 (*J* = 4,8)	7,29...7,58 (3H, m, H_{Ar})	7,69...8,24 (*J* = 8,9)
IVe	2,87...2,92	3,46...3,58	3,74 (*J* = 13,3)	4,56 (*J* = 6,2)	4,83 (*J* = 4,9)	4,97 (*J* = 5,5)	3,70 (3H, s, OCH_3); 3,71 (3H, s, OCH_3) 6,69...6,87 (3H, m, H_{Ar})	7,69...8,24 (*J* = 8,9)
IVf	2,96...3,00	3,49...3,66	4,02 (*J* = 14,1)	4,60 (*J* = 6,1)	4,88 (*J* = 4,8)	5,05 (*J* = 4,7)	6,87...7,43 (3H, m, H_{Het})	7,69...8,25 (*J* = 8,8)

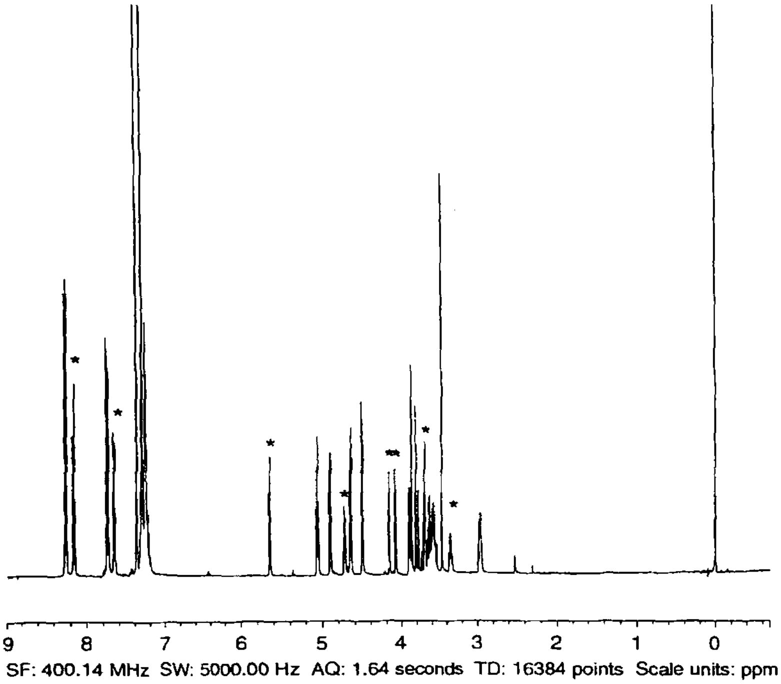


Fig. 1. Spectrum of 63:37 mixture of compounds IVa and Va from the reaction of diol IIIa with paraformaldehyde. Signals of Va are marked with an asterisk.

Oxazolidines IV, according to the PMR spectra of the reaction products, usually are formed together with the isomeric oxazolidines V (for example, see the spectrum in Fig. 1 of the product of the reaction of IIIa with paraformaldehyde, which was recorded immediately after removing of benzene). Boiling of diol IIIb and paraformaldehyde in benzene produces practically pure oxazolidine IVb (Fig. 3). Under the same conditions for the other studied diols, content of the corresponding compound IV in the reaction products varied from 84 to 98%.

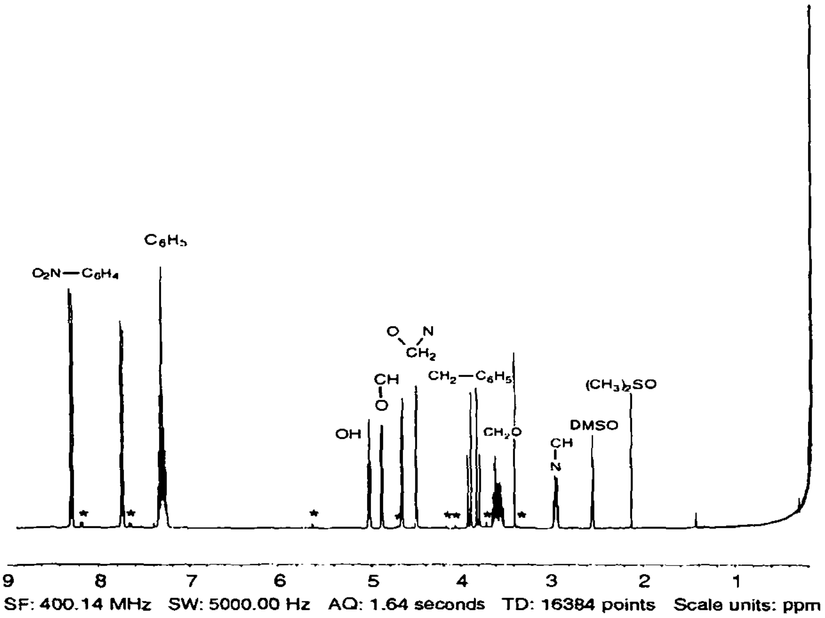


Fig. 2. Spectrum of compound IVa (98% purity). Signals of Va are marked with an asterisk.

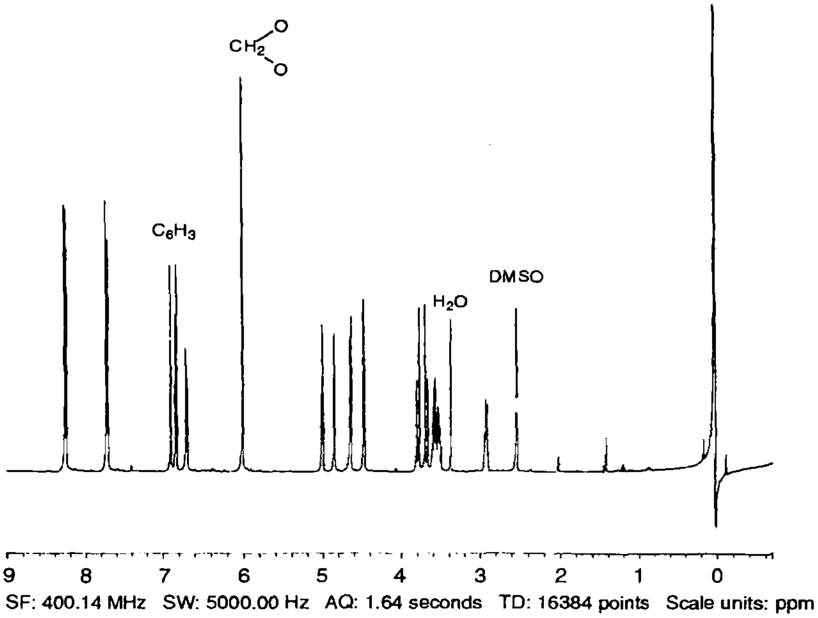


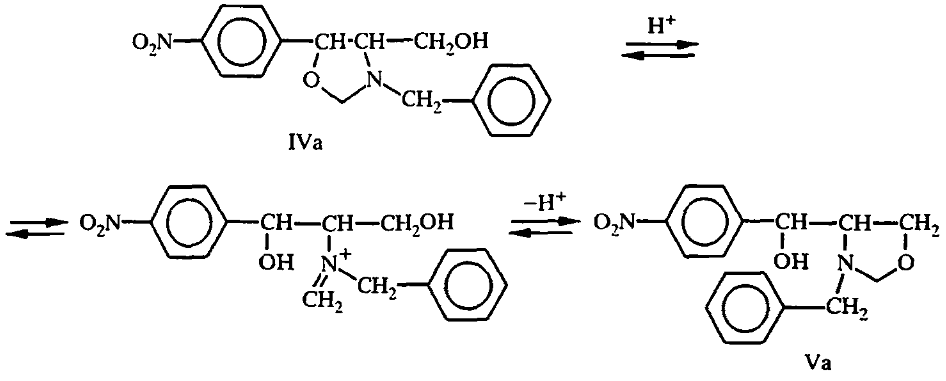
Fig. 3. Spectrum of compound IVb (100% purity).

The presence of oxazolidine V is easily determined from the signals for protons of the $C_6H_4NO_2$, CHOH, CH_2Ar, CH_2O, and CHN moieties (Fig. 1).

The diastereotopic nature of the methylene groups is clearly visible in the PMR spectra of compounds IVa and IVb (Figs. 2 and 3). Thus, the signals for the protons of the OCH_2N and $N\underline{CH_2}C_6H_5$ moieties appear as two quartets whereas signal of the CH_2O protons appears as a more complicated multiplet owing to spin–spin coupling with protons of the hydroxyl and methyne groups.

Interaction of diol IIIa with paraformaldehyde demonstrates that the ratio of products IV and V, in the sample being analyzed immediately after isolation, depends on the reaction conditions. Thus, refluxing of the reagents in toluene for 15 min or in benzene for 15, 30, and 90 min forms a product that contains 92, 43, 54, and 63% of compound IVa, respectively. Crystallization of the initially liquid mixture (45:57) of compounds IVa and Va that was obtained after removing benzene was carried out over 2-3 days and also enabled the shift of equilibrium towards formation of trisubstituted oxazolidine IVa, its content being increased to 97-98%. Holding of a solution of this mixture in deuterated DMSO for 16 days increases the content of compounds IVa to only 69%.

Scheme 2



Thus, the studied reaction is reversible. Compound Va is a product controlled by kinetics whereas IVa is a product controlled by thermodynamics of reaction (Scheme 2).

Table 1 lists the properties of the synthesized oxazolidines IVa-h. Table 2 contains PMR spectral data.

EXPERIMENTAL

PMR spectra were recorded on a Bruker AC-400 spectrometer in DMSO-d_6 with TMS as internal standard. The PMR spectra were processed using the computer program MESTREC. The specific rotations in acetone were measured on a Jasco DIP-370 polarimeter. The melting points were measured on a Reichert (system Kofler) apparatus. Column chromatography was performed on a column (3×70 cm) filled with 35-70 μ silica gel (France). The eluent was ethyl acetate–hexane, 3:7.

Schiff bases II were synthesized using the literature method [5] in ethanol or methanol (for IId,e). The solid products IIa-c and IIf-h were filtered off, washed on the filter with ethanol, dried, and used in the subsequent step. Compounds IId,e were not isolated from the reaction mixture.

(1*S*,2*S*)-2-Aryl(hetaryl)amino-1-(4-nitrophenyl)-1,3-propanediols (IIIa-h).

(1*S*,2*S*)-2-Benzylamino-1-(4-nitrophenyl)-1,3-propanediol (IIIa). Compound IIa (12.6 g, 0.042 mol) in methanol (50 ml) was treated portionwise with $NaBH_4$ (0.8 g, 0.21 mol). The reaction mixture was boiled for 15 min. Half of the methanol quantity was evaporated in a rotary evaporator. The solid was dispersed in water. The separated product IIIa crystallized after some time. It was filtered off, washed with water, dried in air, and used in the next step without additional purification. Yield 12.3 g (97%).

The corresponding aminodiols IIIb-h were synthesized in analogous way from compounds IIb-h.

Compounds IIId,e were isolated as oils. Water was decanted from them. Traces of water were carefully removed using filter paper. The products were used in the next step without additional purification.

3-Aryl(hetaryl)methyl-4-hydroxymethyl-5-(4-nitrophenyl)oxazolidines (IVa-h).

(+)-(4*S*,5*S*)-3-Benzyl-4-hydroxymethyl-5-(4-nitrophenyl)oxazolidine (IVa). Mixture of compound IIIa (6.04 g, 0.02 mol) and paraformaldehyde (0.63 g, 0.021 mol) was boiled in benzene in a Dean–Starke apparatus until water was completely distilled. The reaction mixture was passed through filter paper to remove the excess of paraformaldehyde; benzene was distilled off. The solid crystallized after some time. Yield 5.65 g of compound IVa, which was recrystallized from hexane. Oxazolidines IVb-h were synthesized analogously from the corresponding diols IIIb-h.

Compound IVb was purified by recrystallization from hexane. Compounds IVd,e,h were isolated by column chromatography. Compounds IVc,f,g were isolated by column chromatography and then recrystallized from hexane.

The work was performed in the Pharmaceutical Department of the University in Clermont-Ferrand (France).

REFERENCES

1. V. A. Kiyashev, N. B. Leonidov, S. I. Uspenskaya, and V. V. Gatsura, *Ross. Khim. Zh.*, **41**, No. 5, 5 (1997).
2. V. P. Zaitsev, S. Kh. Sharipova, and I. I. Zhuravleva, *Khim. Farm. Zh.*, **32**, 44 (1998).
3. S. Kh. Sharipova and V. P. Zaitsev, *Khim. Farm. Zh.*, **20**, 858 (1986).
4. V. M. Potapov, V. M. Dem'yanovich, V. P. Zaitsev, and S. Kh. Sharipova, *Zh. Org. Khim.*, **23**, 510 (1987).
5. V. M. Potapov, V. M. Dem'yanovich, V. P. Zaitsev, and S. Kh. Sharipova, *Zh. Org. Khim.*, **26**, 2574 (1990).
6. V. P. Zaitsev, P. P. Purygin, and S. Kh. Sharipova, *Khim. Geterotsikl. Soedin.*, No. 10, 1394 (1990).