SYNTHESIS OF 7-HYDROXY-4,5,6,7-TETRAHYDROTHIENO/3,2-c/ PYRIDINE-6-CARBOXYLIC ACIDS AND 4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE-3 CARBOXYLIC ACIDS

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Abstract - This paper deals with the synthesis of 7-hydroxy-4,5,6,7-tetrahydrothieno/3,2-c/pyridine-6-and 4-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids by Pictet-Spengler cyclisation of the corresponding β-thienylserines and β-phenylserines respectively. Their diastereoisomers were separated and identified.

In a previous paper [1] we have reported the synthesis of 7-hydroxy-4,5,6,7-tetrahydrothieno/3,2-c/pyridine-6-carboxylic acid (2a) by Pictet-Spengler cyclisation [2] of threo β-2-thienylserine (1a) with formaldehyde. This compound is used as starting material for the preparation of platelet antiaggregating agents [1].

We wish now to report some experimental modifications which allowed us to isolate both cis (2a) and trans (2b) diastereoisomers. By the same way, we have also prepared cis and trans 4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids. Similar compounds for which cardiovascular properties have been claimed [3] were prepared only by Grethe and al.[4] by following a long multisteps synthesis but the diastereoisomers were not separated.

The Dullaghan-Nord synthesis [5] of β-2-thienylserine (1a) only yielded traces of the erythro diastereoisomer (1b). To obtain this latter isomer in large quantities, we used the Akabori method [6] by condensing cupric glycinate with 2-thienaldehyde in alkaline medium [7]. The β-2-thienylserine diastereoisomers formed in the reaction were separated and purified as follows [7]: the reaction mixture was introduced on a column of sulfonic groups containing resin (Duolite C20); elution with water eliminated non basic constituents ; then aqueous ammoniacal elution yielded the mixture of β-2-thienylserines from which cupric ions were eliminated by chromatographic treatment on an iminodiacetic groups containing resin (Duolite E S 466). After lyophylisation, the major threo diastereoisomer (1a), formed in the 2/1 ratio, was isolated in a pure state by repeated crystallization from water in which it is less soluble. The more soluble erythro diastereoisomer (1b) was isolated from the mother liquor and purified by chromatography on a silica gel column using a mixture of n-butanol/butanone/water/34 % aqueous ammonia in the ratio 5/3/1/1 as eluent.

Both diastereoisomers (1a) and (1b) were then cyclized into thienopyridines (2a) and (2b) by Pictet-Spengler cyclisation with a large excess of formaldehyde in diluted sulfuric acid. Compounds (2a) and (2b) precipitated in reaction medium or after neutralisation with diluted sodium hydroxide.

The same process was then applied to the synthesis of isosteric isoquinolines. The known β-piperonylserine (3) was used as an example [8] since the presence of the electron-donating methylene-

dioxy group would favour the subsequent cyclisation reaction.

Piperonal was condensed with glycine according to Eisele [8] to give diastereoisomeric serine derivatives (3a) and (3b) which were isolated as described above. The ratio of the threo and erythro isomers was 4/1.

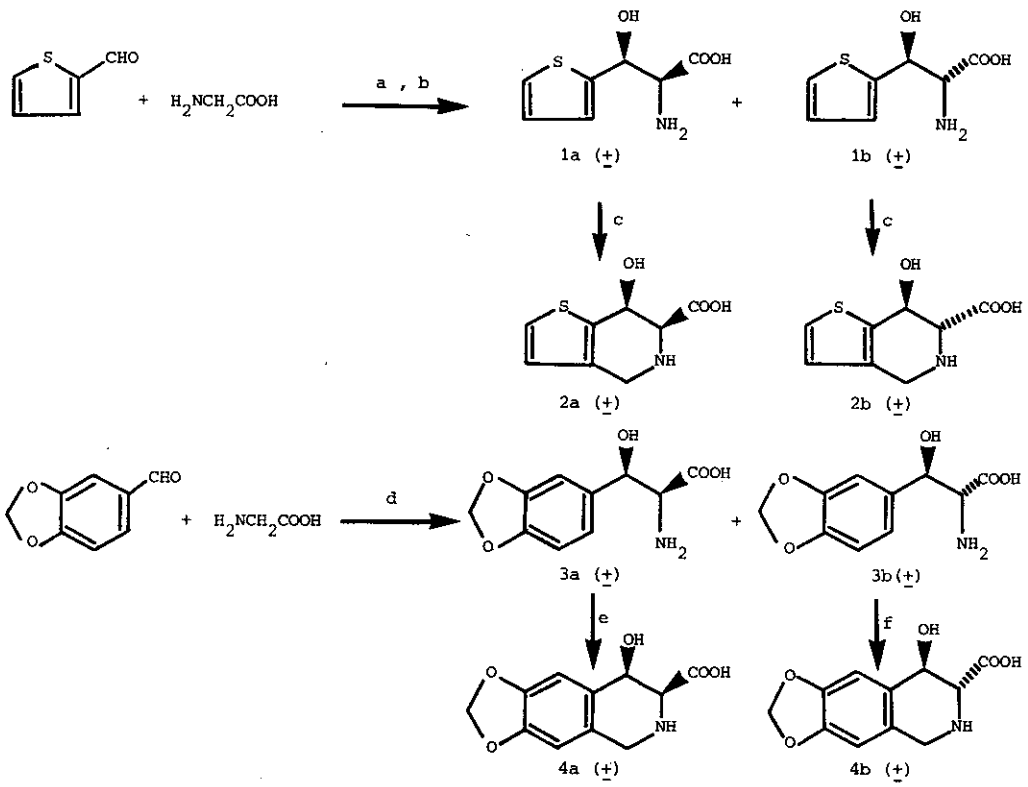
The threo configuration was attributed to the predominant component (3a) by analogy with literature data on β-phenylserines [10] and β-2-thienylserines [6]. Thin layer chromatography of both isomers gave Rf values in accordance with such an attribution.

Compounds (3a) and (3b) were respectively transformed into cis and trans isoquinolines (4a) and (4b). The cyclisation occurred on the activated 6-position as expected by the presence of the methylenedioxy substituant.

NMR data on thienopyridines (2a) and (2b) (Table II) and similar data obtained with some other isoquinoline derivatives [10] allowed us to attribute the smaller coupling constant $J_{H_3-H_4}$ to the cis diastereoisomer (4a) thus confirming the threo configuration of the β-phenylserine (3b) from which it was issued.

Our process of formation of the isoquinolines (4a) and (4b) is quite general and could be applied to various aromatic aldehydes, provided the aromatic nucleus is conveniently activated to allow a Pictet-Spengler cyclisation.

Scheme 1

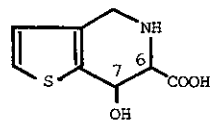
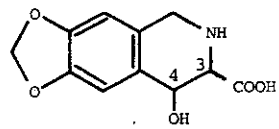


a : 0.5$(CH_3COO)_2Cu$,aq.NaOH(pH≈12.5),r.t.,3h; b : 6N HCl,r.t.,12h ; c : aq.35% HCHO(15éq), 0.25 $\underline{N}$ H_2SO_4,r.t.,72h ; d : aq.NaOH(1.2éq), C_2H_5OH, r.t.,8h ; e : aq.30% HCHO(8éq.),1 $\underline{N}$ H_2SO_4, r.t.,23 h ; f : aq. 30 % HCHO(9.5éq.), 1 $\underline{N}$ H_2SO_4, r.t.,18h.

Table I

Diastereoisomer	Yield %	m.p. °C	IR(KBr) max(cm^{-1})	H NMR (Solvent) δ(ppm) , J (Hz)
1a (threo)	48	183	1640	(D_2O) :4.00(D,J=4.5,1H,CHCOOH) ; 5.56(d, J=4.5),1H,CHOH) ; 7.16(m,2H,arom.); 7.52(m,1H,arom.)
1b (erythro)	24	172	1640	(D_2O) :4.13(d,J=4.0,1H,CHCOOH) ; 5.63(d, J=4.0,1H,CHOH) ; 7.13(m,2H,arom.) ; 7.50(m,1H,arom.)
2a (cis)	73	276	1670	(D_2O+CF_3COOH) : 4.55(m,3H,CH_2NHCHCOOH) ; 5.52(d,J=3.0,1H,CHOH) ; 7.00(d, J=5.5,1H,arom.) ; 7.62(d,J=5.5,1H, arom.)
2b (trans)	30	238	1640	(D_2O+CF_3COOH) : 4.57(m,3H,CH_2NHCHCOOH) ; 5.55(d,J=5.5,CHOH) ; 7.03(d,J=5.5, 1H,arom.) ; 7.67(d,J=5.5,1H,arom.)
3a (threo)	40	200	1650	(D_2O+CF_3COOH) : 4.25(d,J=4.5,1H,CHCOOH) ; 5.32(d,J=4.5,1H,CHOH) ; 5.92(s,2H, OCH_2O) ; 6.92(m,3H,arom.)
3b (erythro)	10	200	1645	(D_2O+CF_3COOH) : 4.35(d,J=4.5,1H,CHCOOH) ; 5.30(d,J=4.5,1H,CHOH) ; 5.92(s,2H, OCH_2O) ; 6.90(s,3H,arom.)
4a (cis)	67	>250	1660	(D_2O+CF_3COOH) : 4.40(m,3H,CH_2NCHCOOH) ; 5.20(d,J=2.6,1H,CHOH) ; 5.95(s,2H, OCH_2O) ; 6.73(s,1H,arom.) ; 6.90(s, 1H,arom.)
4b (trans)	67	>250	1640	(D_2O+CF_3COOH) : 4.50(m,3H,CH_2NCHCOOH) ; 5.20(d,J=4.8,1H,CHOH) ; 5.95(s,2H, OCH_2O) ; 6.70(s,1H,arom.) ; 6.90(s, 1H,arom.)

Table II

	Diastereosiomer	$J_{H_6-H_7}$ (Hz)
	2a (cis)	3.0
	2b (trans)	5.5
		$J_{H_3-H_7}$ (Hz)
	4a (cis)	2.6
	4b (trans)	4.8

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