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Optical Resolution of β-Blockers by HPLC on Cellulose Triphenylcarbamate Derivatives[1)]

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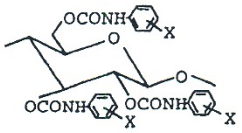
Optical resolution of five β-adrenergic blocking agents (β-blockers) alprenolol, oxyprenolol, propranolol, pindolol, and atenolol was examined by HPLC on 13 chiral stationary phases composing of cellulose triphenylcarbamate derivatives. All β-blockers were completely resolved on a cellulose tris(3,5-dimethylphenylcarbamate) column.

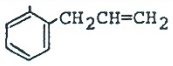
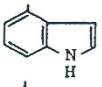
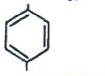
β-Adrenergic blocking agents (β-blockers) are widely-used important drugs for the treatment of hypertension and angina pectoris. Most of β-blockers possess a general structure $ArOCH_2CH(OH)CH_2NHCH(CH_3)_2$ (Ar = aromatic) and have been used in a form of racemic mixtures, although the (S)-isomers are much more effective (50-500-fold) than the (R)-isomers.[2)] To avoid unnecessary stress, or in some cases toxicity, on organism caused by the (R)-isomers, the administration of optically



X =

1: 4-CH_3O	8: 4-CF_3
2: 4-CH_3	9: 4-NO_2
3: 4-CH_3CH_2	10: 3,4-Cl_2
4: H	11: 3-CH_3
5: 4-F	12: 3,4-$(CH_3)_2$
6: 4-Cl	13: 3,5-$(CH_3)_2$
7: 4-Br	

$ArOCH_2\underset{\underset{OH}{|}}{CH}CH_2NHCH(CH_3)_2$

β-Blocker	Ar
Alprenolol	
Oxyprenolol	
Propranolol	
Pindolol	
Atenolol	

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pure (S)-isomers is desirable. Various preparative methods of the optical isomers have so far been reported.[3] Resolution of β-blocker derivatives have also been effected by HPLC with chiral stationary phases,[4-6] and recently oxyprenolol and propranolol were resolved without derivatization.[7] In this letter, we report the very efficient direct resolution of five β-blockers ($ArOCH_2CH(OH)CH_2NHCH(CH_3)_2$) by HPLC on both analytical and preparative columns packed with cellulose triphenylcarbamate derivatives (1-13) supported on silica gel.[8,9]

Preparation of chiral stationary phases used for analytical resolution has been reported.[8,9] The stationary phase for preparative separation was prepared with silica gel of a large particle size (20 μm) in place of silica gel (10 μm) for analytical chromatography. The resolution was carried out with a JASCO TRIROTAR-II equipped with a JASCO UVIDEC-III UV and DIP-181C polarimetric detectors at 25 °C. Optical rotation was followed in a flow cell (5 x 0.3 (i.d.) cm) with a mercury lamp (no filters). Dead time (t_0) was estimated with 1,3,5-tri-tert-butylbenzene.[10]

Propranolol and pindolol were chromatographed with the chiral columns 1-13 (Table 1). All columns eluted (+)-isomers first and showed better chiral recognition for pindolol than for propranolol except for column 10. Stationary phases 1 and 9 having 4-methoxy and 4-nitro groups, respectively, exhibited no

Table 1. Capacity factors (k_1') of the first-eluting isomer, separation factors (α), and resolution factors (Rs) in the resolution of propranolol and pindolol on chiral columns 1-13[a)]

Stationary Phase		Propranolol			Pindolol		
		k_1'	α	Rs	k_1'	α	Rs
1	4-CH_3O	0.72	1.00		4.51	1.00	
2	4-CH_3	0.73 (+)	1.14	0.58	3.17 (+)	1.28	1.51
3	4-CH_3CH_2	0.60 (+)	1.20	0.67	2.47 (+)	1.38	1.84
4	H	0.95 (+)	1.05		4.75 (+)	1.21	0.98
5	4-F	0.65 (+)	1.10	0.40	3.22 (+)	1.27	1.27
6	4-Cl	0.64 (+)	1.23	0.68	2.79 (+)	1.43	2.00
7	4-Br	0.64 (+)	1.26	0.97	2.81 (+)	1.47	2.58
8	4-CF_3	0.50 (+)	1.40	2.07	2.60 (+)	1.57	2.69
9	4-NO_2	0.87	1.00		4.77	1.00	
10	3,4-Cl_2	0.72 (+)	1.70	2.70	1.71 (+)	1.61	1.53
11	3-CH_3	0.67 (+)	≈ 1		3.07 (+)	1.17	0.79
12	3,4-$(CH_3)_2$	1.15 (+)	1.36	1.37	3.19 (+)	4.58	7.25
13	3,5-$(CH_3)_2$	1.43 (+)	2.29	5.56	3.17 (+)	5.07	>3

a) Column: 25 x 0.46 (i.d.) cm, eluent: hexane-2-propanol-diethylamine (80:20:0.1), 0.5 ml/min. k_1' = (retention time of the first-eluting isomer - dead time (t_0)) / t_0 ; α = (capacity factor of second-eluting isomer) / k_1' ; Rs = 2 x (difference of retention times of the second- and first-eluting isomers) / (sum of the band widths of the first- and second-eluting isomers)

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chiral recognition ability. The reason for the low ability of these stationary phases have been discussed.[9] It has been shown that introduction of both electron-donating and -withdrawing substituents tends to improve the optical resolution ability of the stationary phases compared with 4.[9] In the present study, disubstituted carbamates 10, 12, and 13, particularly the last one, also showed better ability of optical resolution. Cellulose tris(3,5-dichlorophenylcarbamate)[9] would efficiently resolve these β-blockers. However,

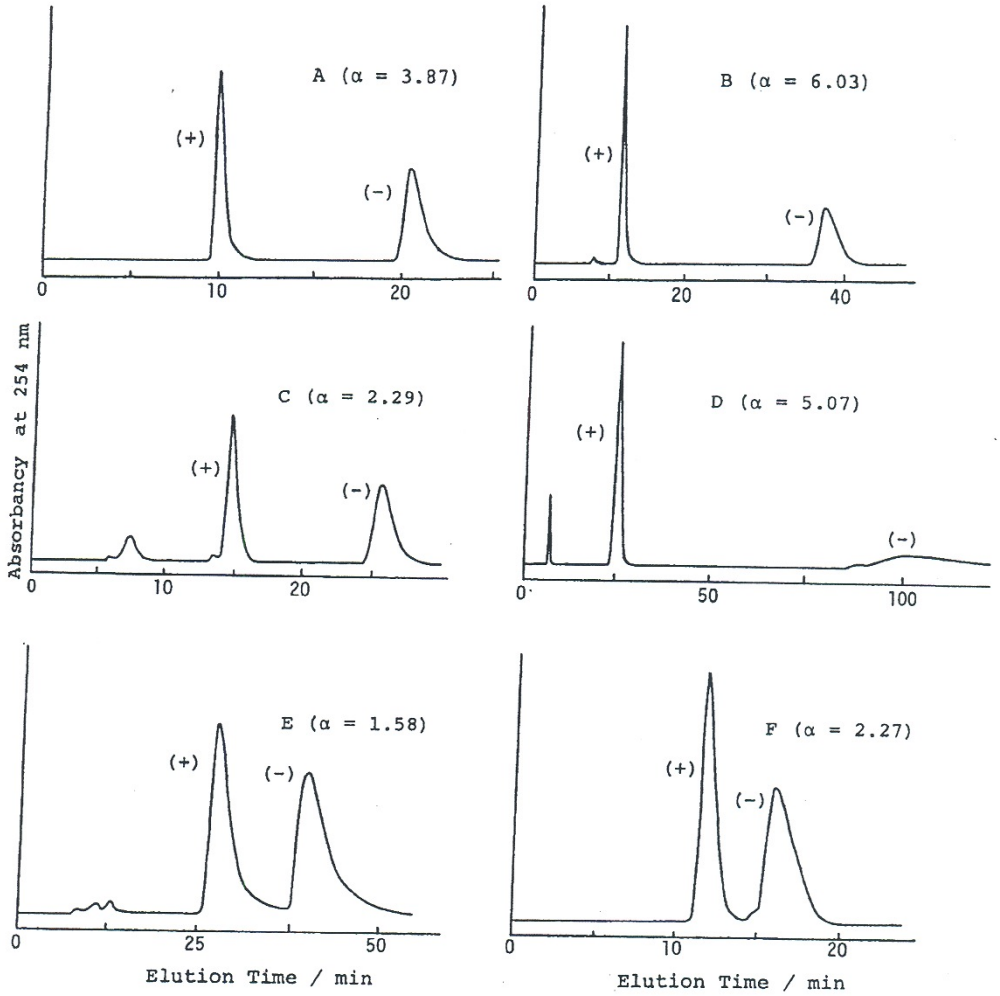

Fig. 1. Resolution of β-blockers (A,F: alprenolol, B: oxyprenolol, C: propranolol, D: pindolol, E: atenolol) on cellulose tris(3,5-dimethylphenylcarbamate) columns. Column: A-E, 25 x 0.46 (i.d.) cm; F, 50 x 2.0 (i.d.) cm. Eluent: A, hexane-2-propanol (90:10); B-F, hexane-2-propanol-diethylamine (80:20:0.1).

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this could not be used under the present chromatographic conditions because it was slightly dissolved in the eluents.

Chromatograms of the resolution of the five β-blockers on 13 are shown in Fig. 1. The β-blockers were resolved very effectively giving high α values. These α values are much larger than those for oxyprenolol (1.25) and for propranolol (1.13) reported recently.[7] The (+)-isomers, which may be assigned to R configuration,[11] were eluted first in all cases. Many racemic alcohols have been resolved most effectively on 13.[9] Hydrogen bonding between the hydroxy group of the β-blockers and the carbonyl group of 13 seems to play the most important role for effective chiral recognition. The hydrogen bonding may be strongest on 13. The addition of a small amount of diethylamine in the eluent led to a decrease in tailing of chromatograms. Rapid exchanges between adsorption and desorption of a β-blocker molecule on the stationary phases seem to be attained by the existence of the amine.

With a preparative column (50 x 2 (i.d.)cm), 150 mg of alprenolol (Fig. 1, F), 100 mg of propranolol, and 400 mg of oxyprenolol were completely resolved in one injection. The column was quite stable. Thus, cellulose tris(3,5-dimethylphenylcarbamate) columns will be valuable not only in analytical sense but also in preparative sense for studies on β-blockers.

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