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

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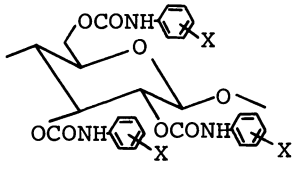
Optical resolution of five β-adrenergic blocking agents (β-blockers) alprenolol, oxyprenolol, propranolol, pindolol, and atenolol was examined by HPLC on 13 chiral stationary phases composing of cellulose triphenylcarbamate derivatives. All β-blockers were completely resolved on a cellulose tris(3,5-dimethylphenylcarbamate)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

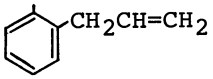
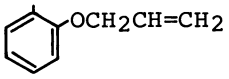
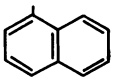
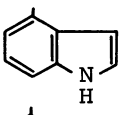
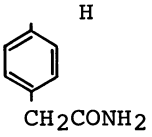
β-Adrenergic blocking agents (β-blockers) are widely-used important drugs for the treatment of hypertension and angina pectoris. Most of β-blockers possess a general structure $ArOCH_2CH(OH)CH_2NHCH(CH_3)_2$ (Ar = aromatic) and have been used in a form of racemic mixtures, although the (S)-isomers are 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
2: 4-CH_3
3: 4-CH_3CH_2
4: H
5: 4-F
6: 4-Cl
7: 4-Br
8: 4-CF_3
9: 4-NO_2
10: 3,4-Cl_2
11: 3-CH_3
12: 3,4-$(CH_3)_2$
13: 3,5-$(CH_3)_2$

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

β-Blocker	Ar
Alprenolol	
Oxyprenolol	
Propranolol	
Pindolol	
Atenolol	

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)

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,

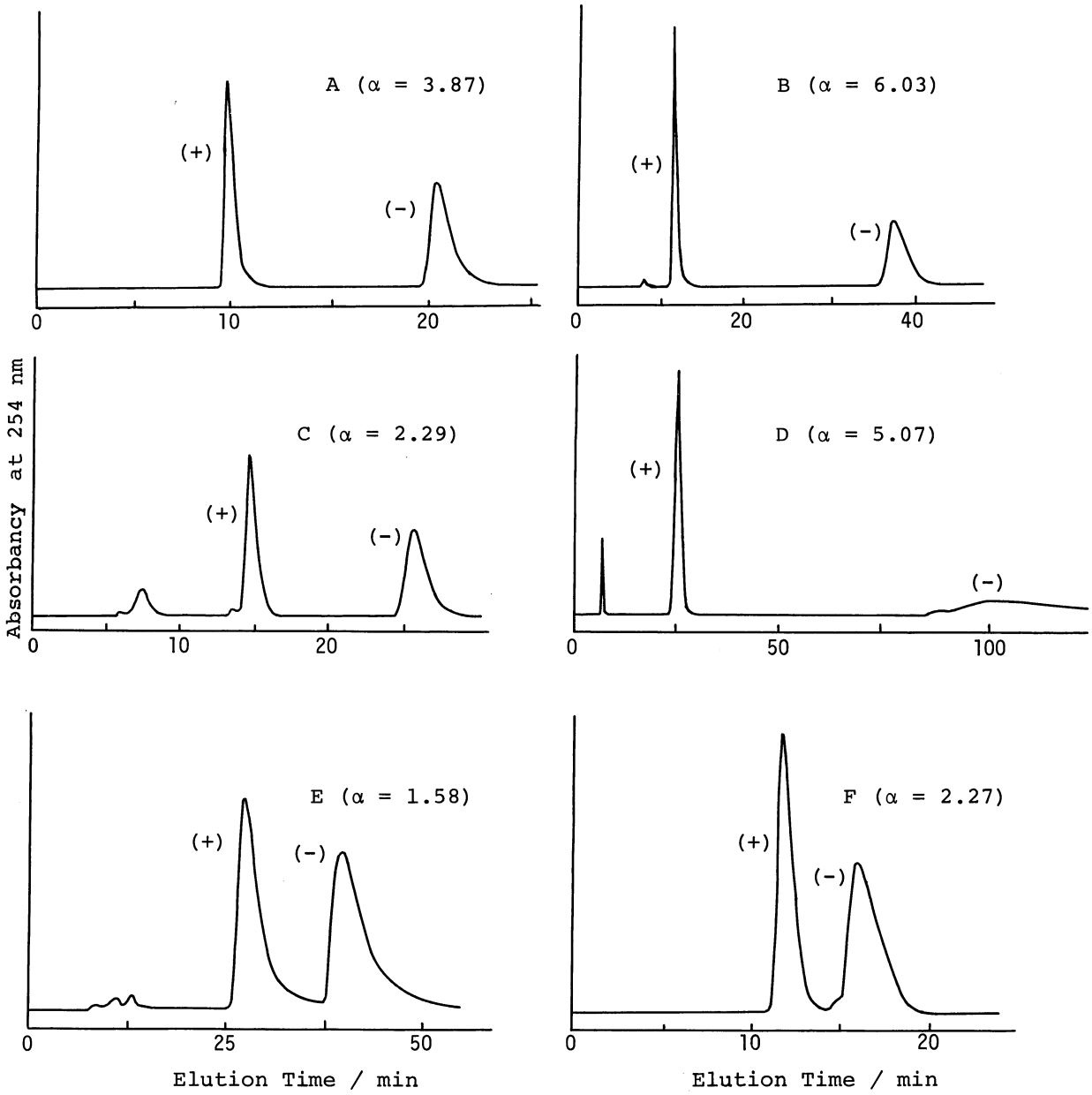


Fig. 1. Resolution of β-blockers (A,F: alprenolol, B: oxyprenolol, C: propranolol, D: pindolol, E: atenolol) on cellulose tris(3,5-dimethylphenylcarbamate) columns. Column: A-E, 25 x 0.46 (i.d.) cm; F, 50 x 2.0 (i.d.) cm. Eluent: A, hexane-2-propanol (90:10); B-F, hexane-2-propanol-diethylamine (80:20:0.1).

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 1~3 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 1~3.[9] Hydrogen bonding between the hydroxy group of the β-blockers and the carbonyl group of 1~3 seems to play the most important role for effective chiral recognition. The hydrogen bonding may be strongest on 1~3. 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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References

1) Chromatographic Resolution 12. For Part 11, see ref. 9.
2) W. L. Nelson and T. R. Burke, Jr., J. Org. Chem., 43, 3641 (1978) and references cited therein.
3) S. Hamaguchi, J. Hasegawa, H. Kawaharada, and K. Watanabe, Agric. Biol. Chem., 48, 2055 (1984) and references cited therein.
4) W. H. Pirkle, J. M. Finn, J. L. Schreiner, and B. C. Hamper, J. Am. Chem. Soc., 103, 3964 (1981).
5) I. W. Wainer, T. D. Doyle, K. H. Donn, and J. R. Powell, J. Chromatogr., 306, 405 (1984).
6) J. Hermansson, J. Chromatogr., 325, 379 (1985).
7) G. Schill, I. W. Wainer, and S. A. Barkan, J. Liq. Chromatogr., 9, 641 (1986).
8) Y. Okamoto, M. Kawashima, and K. Hatada, J. Am. Chem. Soc., 106, 5357 (1984).
9) Y. Okamoto, M. Kawashima, and K. Hatada, J. Chromatogr., in press.
10) H. Koller, K. H. Rimbock, and A. Mannschreck, J. Chromatogr., 282, 89 (1983).
11) M. Dukes and L. H. Smith, J. Med. Chem., 14, 326 (1971).

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