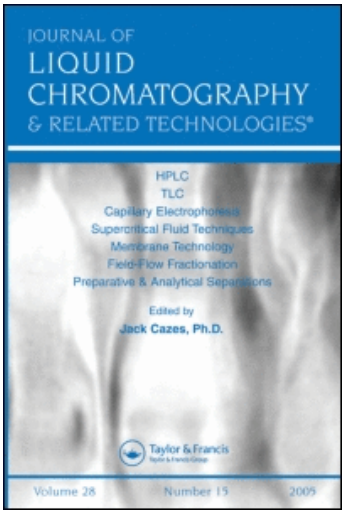

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Optical Resolution of Racemic Drugs by Chiral HPLC on Cellulose and Amylose Tris(phenylcarbamate) Derivatives

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To cite this Article Okamoto, Yoshio , Aburatani, Ryo , Hatano, Kazuhiro and Hatada, Koichi(1988) 'Optical Resolution of Racemic Drugs by Chiral HPLC on Cellulose and Amylose Tris(phenylcarbamate) Derivatives', Journal of Liquid Chromatography & Related Technologies, 11: 9, 2147 — 2163
To link to this Article: DOI: 10.1080/01483918808069046
URL: http://dx.doi.org/10.1080/01483918808069046

JOURNAL OF LIQUID CHROMATOGRAPHY, 11(9&10), 2147-2163 (1988)

OPTICAL RESOLUTION OF RACEMIC DRUGS BY CHIRAL HPLC ON CELLULOSE AND AMYLOSE TRIS(PHENYLCARBAMATE) DERIVATIVES

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ABSTRACT

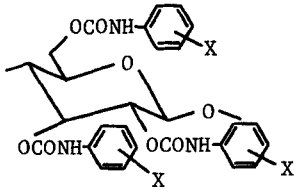
The optical resolution of racemic drugs was performed by high performance liquid chromatography using cellulose and amylose tris(phenylcarbamate) derivatives as chiral stationary phases. Many compounds were effectively resolved by cellulose and/or amylose derivatives having substituents such as methyl, tert-butyl or halogen, on the phenyl groups.

INTRODUCTION

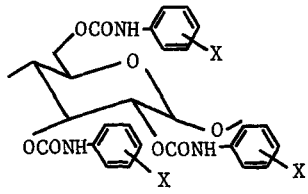
Many enantiomeric pharmaceuticals bearing asymmetric centers often display different activities in biological systems. To avoid side effects caused by one of enantiomers, it is desirable to use drugs in optical pure forms. Many medicines have been used as

racemic mixtures mainly because of difficulty of obtaining optical pure isomers. However, the drugs which will be developed hereafter must be optically pure. Optical resolution of racemic compounds is one of the most important methods for obtaining optical isomers, although this has been considered very laborious.

Recently various chiral columns for high-performance liquid chromatography (HPLC) are commercialized (1), and some of them are known to be useful for optical resolution of racemic drugs. These include the columns of human plasma protein α_1-acid glycoprotein (2), bovine serum albumin (3) and



Cellulose Tris(phenylcarbamate) Derivatives
(X = 3,5-$(CH_3)_2$, 3,5-Cl_2,
3,5-F_2, or 4-tert-C_4H_9)



Amylose Tris(phenylcarbamate) Derivatives
(X = 3,5-$(CH_3)_2$, 3,5-Cl_2, or 3,4,5-$(CH_3)_3$)

optically active polyacrylamide and polymethacrylamide gel (4) as chiral components. The protein columns are usable only for analytical purpose. On the other hand, we recently reported that various cellulose (5,6) and amylose (7) tris(phenylcarbamate) derivatives carrying substituents on the phenyl group, can resolve rather wide range of racemic compounds including β-blocking agents (8) and silyl ethers of 4-hydroxy-2-cyclopentenone used for the synthesis of prostaglandins (9). In this article we would like to report the direct optical resolution of various racemic drugs by HPLC on these polysaccharide columns.

EXPERIMENTAL

Polysaccharide phenylcarbamate derivatives were synthesized by the reaction of polysaccharides and substituted isocyanates in pyridine, and isolated as methanol-insoluble part (5,7). Macroporous silica gel (Merck, LiChrospher SI 4000 or Macherey-Nagel Nucleosil 4000-7) was treated with 3-aminopropyltriethoxysilane in benzene. The polysaccharide derivatives dissolved in tetrahydrofuran were adsorbed on the treated macroporous silica gel about 25 wt/wt %. The packing materials were self-packed in HPLC columns (25 x 0.46 (id) cm) by a slurry method. The chromatographic experiments were performed with a JASCO TRIROTAR-II

liquid chromatograph equipped with UV (JASCO UVIDEC 100-III) and polarimetric detectors. Optical rotation was monitored in a flow cell (50 x 2 (id) mm) at full lamp (Hg) or at 435 nm (Hg).

RESULTS

Table 1 shows the resolution of β-adrenergic blockers on cellulose tris(3,5-dimethylphenylcarbamate) (CDMPC). Alprenolol, atenolol, oxyprenolol, propranolol, and pindolol were completely resolved. Sotalol was not resolved on the column, but on an amylose tris(3,5-dimethylphenylcarbamate) column (Fig. 1). Dichloroisoproterenol was completely resolved on an amylose tris(3,5-dichlorophenylcarbamate) column (7). Propranolol was more efficiently resolved on cellulose tris(3,5-difluorophenylcarbamate) (α = 2.77) than CDMPC (Fig. 2). Acebutolol was not resolved on cellulose and amylose derivatives.

Table 2 shows the resolution of other antagonists on a CDMPC column. Phenolic compounds like synephrine, isoproterenol, and epinephrine were not eluted from the column when a hexane-2-propanol mixture was an eluent. By the addition of acid like trichloroacetic acid in the eluting system, isoproterenol and epinephrine were resolved into two peaks. Synephrine was not eluted

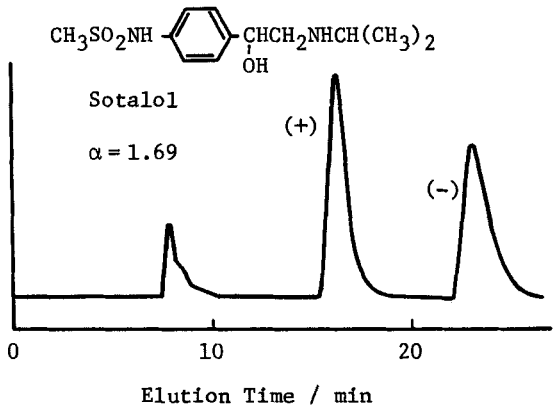


FIGURE 1. Resolution of sotalol on an amylose tris(3,5-dimethylphenylcarbamate) column. (Eluent: hexane-2-propanol-$HNEt_2$ (80:20:0.1); 0.5 ml min^{-1})

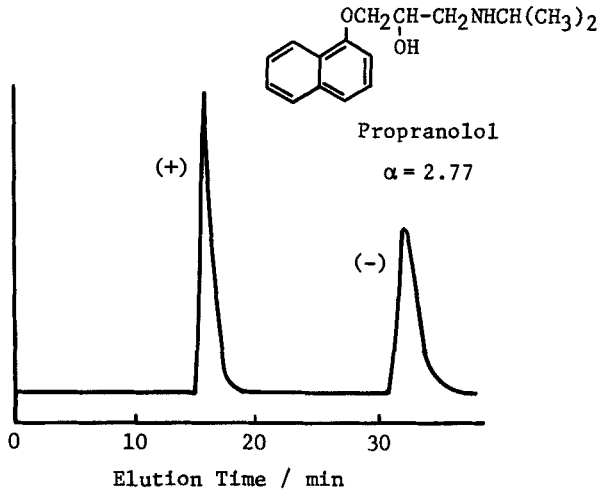
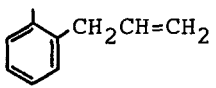
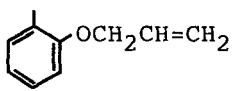
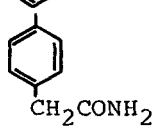
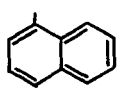
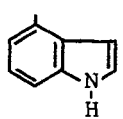


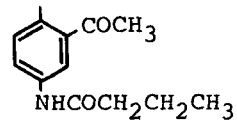
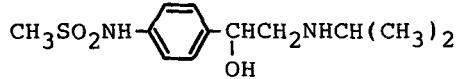
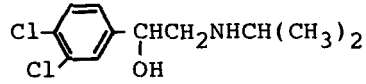
FIGURE 2. Resolution of propranolol on a cellulose tris(3,5-difluorophenylcarbamate) column. (Eluent: hexane-2-propanol (90:10); 0.5 ml min^{-1})

TABLE 1

Optical Resolution of β-blockers

on a Cellulose Tris(3,5-dimethylphenylcarbamate)[a]

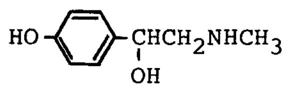
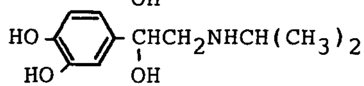
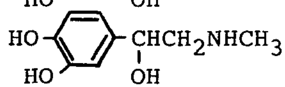
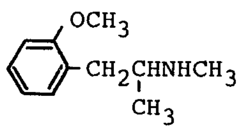
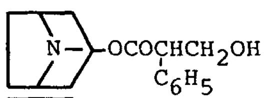
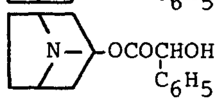
$\underset{\text{Ar}}{\overset{}{\text{O}}}\text{CH}_2\underset{\text{OH}}{\overset{}{\text{CH}}}\text{CH}_2\text{NHCH}(\text{CH}_3)_2$		k_1'[b]	α[c]	Rs[d]
Ar = 	Alprenolol	0.64(+)	3.87	6.88
	Oxyprenolol	0.87(+)	6.03	8.69
	Atenolol	3.54(+)	1.58	1.97
	Propranolol	1.43(+)	2.29	5.56
	Pindolol	3.17(+)	5.07	>3

Ar = 	Acebutolol	2.49	1.00	
	Sotalol	2.50	1.00	
		1.62(+)[e]	1.69	2.97
	Dichloro-isoproterenol[f]	0.85(+)	~1	
		3.08(+)[g]	1.82	4.13

[a]Eluent: hexane-2-propanol-$HNEt_2$ (80:20:0.1), 0.5 ml/min. [b]Capacity factor of the first eluted isomer = (retention time of the first eluted isomer - dead time) / dead time. [c]Separation factor = (capacity factor of the second eluted isomer) / k_1'. [d]Resolution factor = 2 x (difference of retention times of (+) and (-) isomers) / (the band width of the two peaks). [e]An amylose tris(3,5-dimethylphenylcarbamate) column was used. [f]Eluent: hexane-2-propanol (98:2). [g]An amylose tris(3,5-dichlorophenylcarbamate) column was used.

TABLE 2

Resolution of Antagonists on a Cellulose Tris(3,5-dimethylphenylcarbamate) Column

Racemic Drugs		Eluent[a]	k'_1	α	Rs
Adrenergic Agent					
	Synephrine	D	not eluted		
	Isoproterenol	D	1.12(+)	1.28	0.56
	Epinephrine	D	4.51	1.10	
	Methoxyphenamine	A	1.53(+)	1.41	1.66
Antimuscarinic Drug					
	Atropine	C	0.72(+)	1.62	2.30
	Homatropine	C	0.84(+)	3.13	5.78

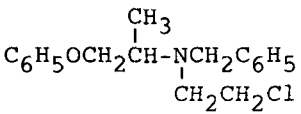
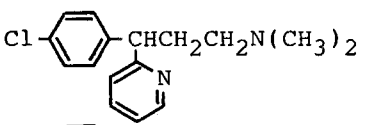
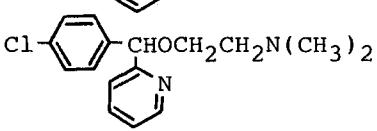
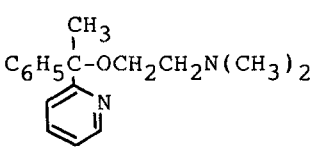
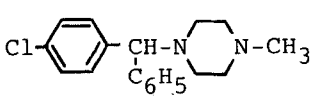
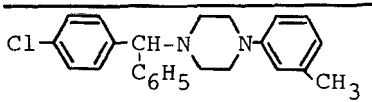
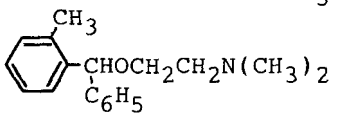
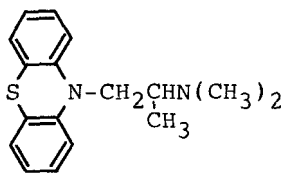
Antihypertensive					
	Phenoxybenzamine	B	0.70(-)	1.13	0.70
Antihistaminic					
	Chlorpheniramine	A	1.75(-)	1.09	0.61
	Carbinoxamine	B	0.98(+)	1.31	0.66
	Doxylamine	A	1.80(+)	1.27	0.86
	Chlorcyclizine	A	0.64(+)	1.21	0.63

Table 2. continued

TABLE 2. continued

	Meclizine	A	1.20	1.00	
	Orphenadrine	B	0.56(+)	1.89	2.11
	Promethazine	A	0.88	1.00	
		A	1.84(+)[b]	1.24	1.47

[a]A: hexane-2-propanol (98:2), B: hexane-2-propanol (90:10), C: hexane-2-propanol-$HNEt_2$ (80:20:0.1), D: hexane-2-propanol-CCl_3COOH (80:15:5).

[b]An Amylose tris(3,5-dichlorophenylcarbamate) column was used.

even in this eluting system. More addition of trichloroacetic acid or 2-propanol damaged the column. Synephrine was eluted from the column of cellulose tris(3,5-dimethylphenylcarbamate) chemically bounded to silica gel (10) when hexane-2-propanol-HCOOH (60:35:5) was used as eluent, but no separation was achieved.

Promethazine which was not resolved on cellulose derivatives were completely resolved on amylose tris(3,5-dichlorophenylcarbamate) (7). A new carbamate, cellulose tris(4-tert-butylphenylcarbamate), could more effectively resolve chlorcyclizine than CDMPC (Fig. 3).

Figures 4-7 show the resolution of other 12 racemic drugs on cellulose and amylose tris(phenylcarbamate) derivatives. Though CDMPC often exhibits high resolving abilities for many compounds (6), it could separate only mephenesin, diltiazem and warfarin. Other drugs were resolved on the cellulose tris(phenylcarbamate) derivatives carrying substituents such as 3,5-Cl_2, 3,5-F_2, 4-tert-C_4H_9, or 3,4,5-$(CH_3)_3$.

A calcium antagonist, nicardipine was completely resolved on a cellulose tris(4-tert-butylphenylcarbamate) (Fig. 5-A). Xylan bis(3,5-dichlorophenylcarbamate) (11) also showed good resolving ability for nicardipine (Fig. 5-B). The elution order of nicardipine on xylan bis(3,5-dichlorophenylcarbamate)

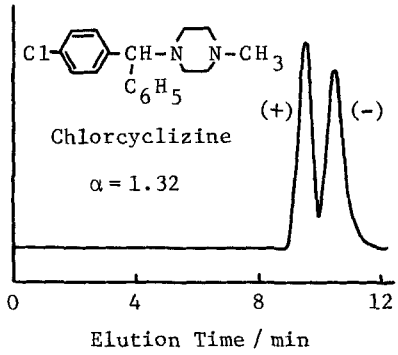


FIGURE 3. Optical resolution of chlorcyclizine on a cellulose tris(4-tert-butylphenylcarbamate) column. (Eluent: hexane-2-propanol (98:2); 0.5 ml min^{-1})

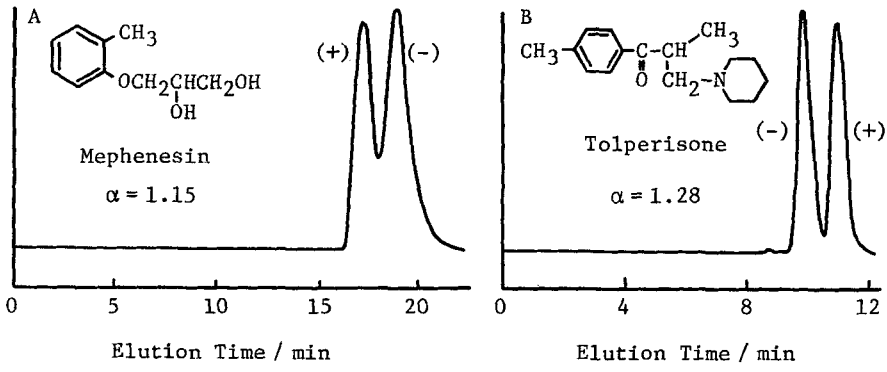


FIGURE 4. Optical resolution of racemic drugs used as a relaxant on cellulose tris(3,5-dimethylphenylcarbamate) (A) and cellulose tris(3,5-difluorophenylcarbamate) (B). (Eluent: A: hexane-2-propanol-$HNEt_2$ (80:20:0.1); B: hexane-2-propanol (90:10); 0.5 ml min^{-1})

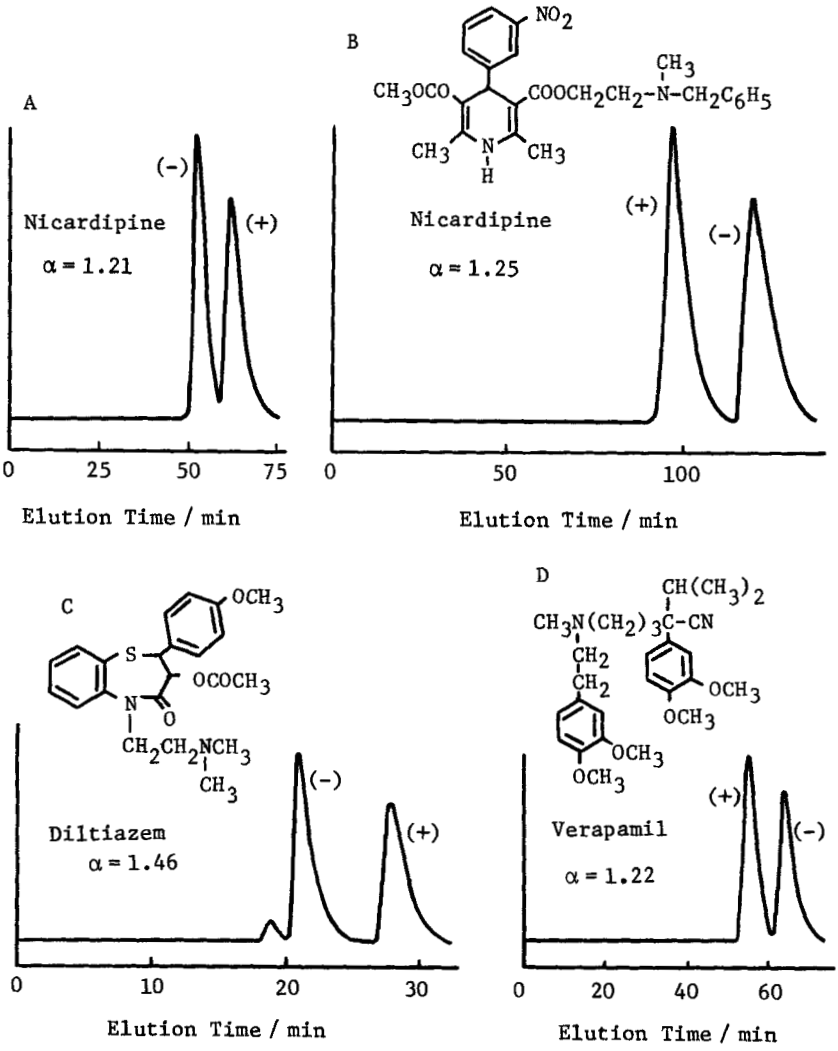


FIGURE 5. Optical resolution of racemic drugs used as calcium antagonist. (Column: A: cellulose tris(4-tert-butylphenylcarbamate); B: xylan bis(3,5-dichlorophenylcarbamate); C: cellulose tris(3,5-dimethylphenylcarbamate); D: cellulose tris(3,5-difluorophenylcarbamate); eluent: A-C: hexane-2-propanol (90:10); D: hexane-2-propanol-$HNEt_2$ (80:20:0.1); 0.5 ml min^{-1})

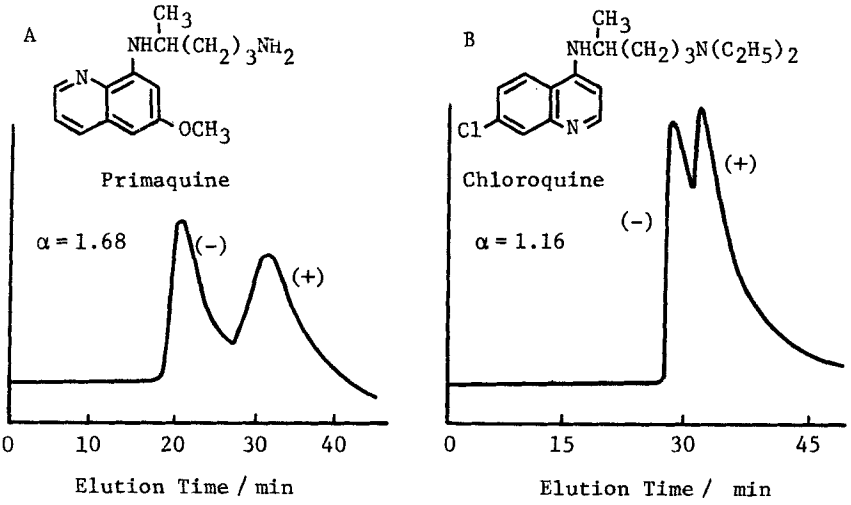
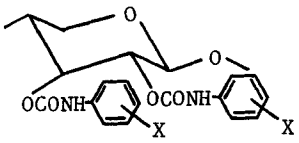


FIGURE 6. Optical resolution of anti-malarial drugs on a cellulose tris(4-tert-butylphenylcarbamate) column. (Eluent: A: hexane-2-propanol-$HNEt_2$ (80:20:0.1); B: hexane-2-propanol (90:10); 0.5 ml min^{-1})



X = 3,5-Cl_2

Xylan Bis(3,5-dichlorophenylcarbamate)

was opposite to that on cellulose tris(4-tert-butylphenylcarbamate).

Antimalarial drugs, chloroquine and primaquine, were resolved on a cellulose tris(4-tert-butylphenylcarbamate) column (Fig. 6). Other polysaccharide phenylcarbamate derivatives could not resolve them.

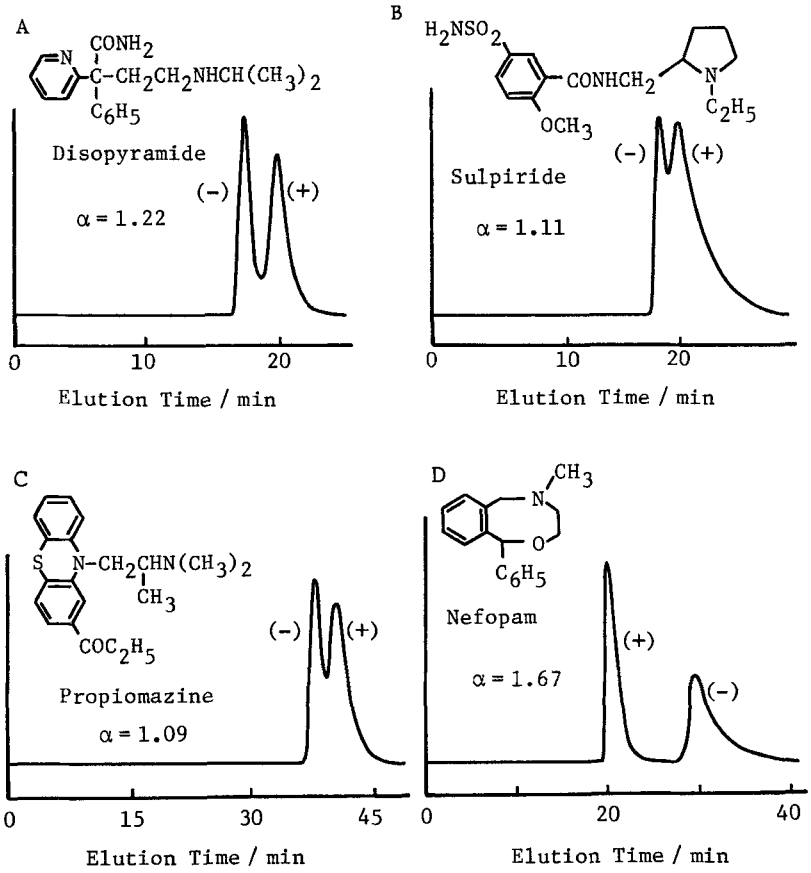


FIGURE 7. Optical resolution of five drugs. (Column: A: amylose tris(3,5-dichlorophenylcarbamate); B: amylose tris(3,5-dimethylphenylcarbamate); C: amylose tris(3,4,5-trimethylphenylcarbamate); D: cellulose tris(3,5-dichlorophenylcarbamate); E: cellulose tris(3,5-dimethylphenylcarbamate); eluent: A: hexane-ethanol (70:30); B: hexane-ethanol (80:20); C: hexane-2-propanol (98:2); D: hexane-2-propanol (95:5); E: hexane-2-propanol-HCOOH (80:20:1); 0.5 ml min^{-1})

(continued)

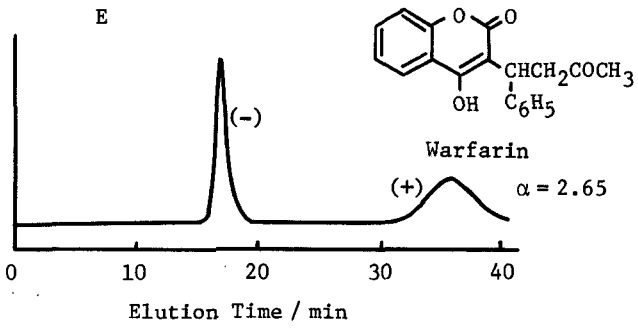


FIG. 7 (continued)

Various racemic drugs were resolved on cellulose and amylose tris(phenylcarbamate) derivatives adsorbed on silica gel. Since these chiral stationary phases were quite stable under the present experimental conditions, we can use these columns not only analytically but also preparatively.

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