

CINCHONA ALKALOIDS FOR PREPARING NEW, EASILY ACCESSIBLE CHIRAL STATIONARY PHASES. I.  
11-(10,11-DIHYDRO-6'-METHOXY-CINCHONAN-9-OL)-TIOPROPYLSILANIZED SILICA.

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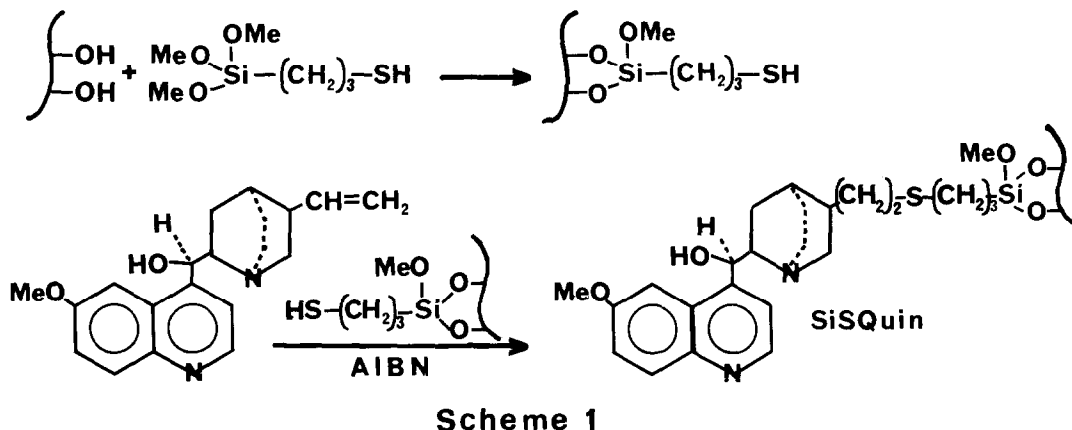
Summary. By reaction of mercatopropylsilanized silica with quinine in the presence of AIBN as radical initiator, a silica supported alkaloid can be obtained, which is effective in the HPLC resolution of racemic arylalkylcarbinols and binaphthol derivatives.

Since the first example of resolution through formation of diastereoisomeric salts by Pasteur who used (1) quinicine and cinchonine, derivatives of the naturally occurring alkaloids quinine and cinchonine respectively, Cinchona alkaloids have been largely employed (2) for the separation of racemic compounds. Besides this application, only a few examples are known in which Cinchona alkaloids have been also used to prepare dissymmetric sorbents for the chromatographic resolution of racemates (3).

These indications induced us to study in a systematic way the possibility of employing Cinchona alkaloids in the preparation of new chiral stationary phases. The complex chiral structure of such compounds suggests that they could be suitable for this purpose: different functional groups (a secondary hydroxyl group, two nitrogen atoms with different basic characteristics, a heteroaromatic ring) in a bulky chiral system could offer multiple interaction points, for a large variety of chiral substrates, A, with a consequent, possible discrimination between the two enantiomers, (+)-A and (-)-A (4). Aim of the present work was to prepare a novel chiral stationary phase by derivatizing a commercial silica with one of the Cinchona alkaloids in such a way that the most important functional groups of these compounds were still present and test the capacity of this material in resolving racemates.

A recent report (5), in which the selective and quantitative reaction of the vinyl group of the above molecules with thiols to give the corresponding sulphides is described, prompted

the preparation of a stationary phase having the above characteristics (Scheme 1).



LiChrosorb SI 60 (Merck, 5 $\mu$ , 4.8 g) was treated with 21 ml of (3-mercaptopropyl) trimethoxysilane in 20 ml of anhydrous 1:1 pyridine/toluene. The slurry was heated at 90°C for 24 hours. After centrifugation the solid was washed (toluene, acetone, diethyl ether, pentane) and dried under vacuum. This derivatized silica was suspended in chloroform and refluxed with quinine (3.2 g) and  $\alpha, \alpha'$ -azoisobutyronitrile (AIBN, 164 mg), as radical initiator, for 30 hours. Again, after centrifugation, the solid was exhaustively washed with methanol until the quinine in excess was completely removed. A 4.6 x 250 mm column was slurry packed (carbon tetrachloride) with this derivatized silica (SiSQuin) using conventional techniques.

Different racemic arylalkylcarbinols and binaphthol derivatives have been resolved on this column and results are reported in Table 1 and 2 respectively. In the figure the u.v. detection of two resolutions is shown, as representative examples. All the compounds studied are satisfactorily resolved on the above chiral stationary phase. It is interesting to note that the  $\alpha$  values reported for several of the compounds 1-16 are similar to the values obtained for the same compounds by Pirkle and coworkers (6,7). In addition the column efficiency does not vary with time: after a month of continuous runs, the resolution factors  $\alpha$  were the same for the molecules used as test compounds.

It is difficult, at the present time, to propose a model for the interaction of the substrate with the chiral stationary phase, i.e. a chiral discrimination mechanism. However it is interesting to note that the resolution factor  $\alpha$  of the arylalkylcarbinols Ar-CH(R)-OH increases with the bulkiness of R (consider the values for 1,2,3) and it is not affected, at least to a large extent, by the nature of the Ar group. The retention ( $k_1$  values) is particularly high in the case of 9 and 10, for which a more polar eluent had to be used. Steric effects are more evident in the resolution of the binaphthol derivatives: passing from 11 to the bulky derivative 16 a strong reduction of the  $k_1$  value can be observed and on the contrary the resolution factor increases in a clear way (Table 2).

In conclusion this paper shows that quinine can be used to resolve organic racemates other than the ones containing carboxyl groups, as it is characteristic of classical resolution procedures by diastereoisomeric salts formation. A new chiral stationary phase, which is efficient in the resolution of racemic arylalkylcarbinols and binaphthol derivatives, can be easily prepared from the above chiral natural compound. The low cost of the column and its stability in the use, make it of great interest for LC resolution of racemates. Work is now in progress to establish elution order from this column, try to understand chiral discrimination mechanism(s), improve the performances of stationary phases derived from Cinchona alkaloids and to extend the application of these materials to other classes of organic compounds.

TABLE 1. Resolution<sup>a)</sup> of arylalkylcarbinols of general formula ArCH(R)OH.

Compd.	Ar	R	k <sub>1</sub> <sup>b)</sup>	α <sup>b)</sup>
1 <sup>c)</sup>	phenyl	CH <sub>3</sub>	7.3 (5.5)	1.0 (1.05)
2	"	i-Pr	4.8 (2.6)	1.08(1.10)
3	"	t-Bu	3.1 (2.1)	1.10(1.08)
4	p-methoxyphenyl	"	5.7	1.05
5	p-chlorophenyl	"	5.4	1.05
6	p-tolyl	"	2.3	1.07
7	3,4-dichlorophenyl	"	5.5	1.07
8	p-(N,N-dimethyl-phenyl)	"	5.5	1.05
9	phenyl	CF <sub>3</sub>	7.4 (5.3)	1.03(1.06)
10	9-anthryl	CF <sub>3</sub>	6.7 (5.5)	1.11(1.33)

a) The chromatographic resolutions were performed on a Jasco Twinkle apparatus, equipped with a Uvidec 100V detector at 254 nm. Eluent: 2-propanol in hexane, 1% for compounds 1-8, 2% for 9 and 10% for 10. Flow 1 ml/min.

b) In parenthesis are reported the values obtained by Pirkle et al. (6).

c) A partial resolution is observable by circular dichroism detection.

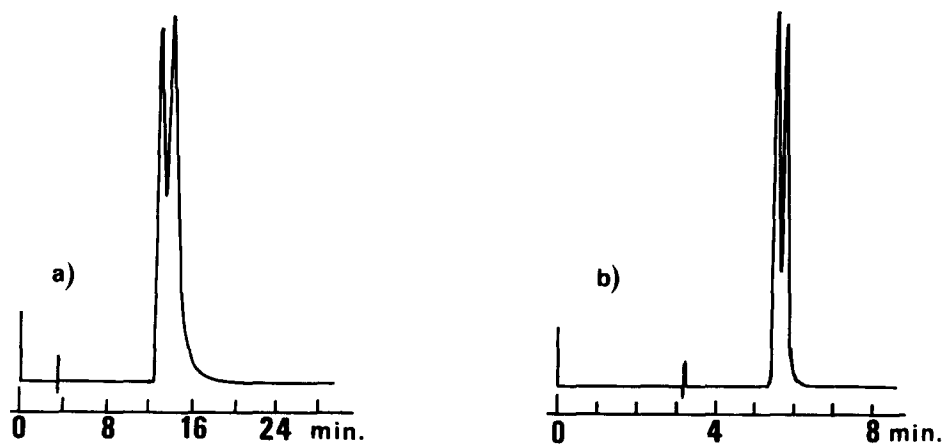
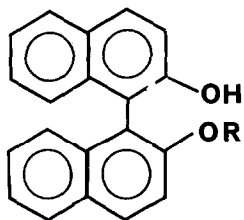


Figure - Chromatographic resolution on SiSquin detected by a Jasco Uvidec 100V at 254 nm.

a) compound 10 (eluent: 2-propanol in hexane, 10%; flow, 1 ml/min).

b) compound 16 (eluent: acetonitrile; flow, 1 ml/min).

TABLE 2. Resolution<sup>a)</sup> of binaphthol derivatives of general formula

Compd.	R	$k_1$ <sup>b)</sup>	$\alpha$ <sup>b)</sup>
11	H	3.9 (17.4)	1.10(1.33)
12	Me	1.0 (3.8) †	1.08(1.53)
13	n-Bu	0.9 (1.4)	1.11(1.17)
14	n-C <sub>12</sub> H <sub>25</sub>	1.3	1.10
15	allyl	0.8 (2.3)	1.09(1.21)
16	i-Pr	0.7 (1.4)	1.16(1.14)

a) The chromatographic resolutions were performed on a Jasco Twinckle apparatus, equipped, with a Uvidex 100V detector, at 254 nm. Eluent: acetonitrile, flow 1 ml/min.

b) In parenthesis are reported the values obtained by Pirkle et al (7).

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