Communications to the Editor

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NEW TYPE OF DERIVATIZATION REAGENTS FOR LIQUID CHROMATOGRAPHIC RESOLUTION OF ENANTIOMERIC HYDROXYL COMPOUNDS

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Two sensitive chiral derivatization reagents, (+)- and (-)-2-methyl-1,1'-binaphthalene-2'-carbonyl nitriles, have been newly developed. These were prepared from dimethyl 1,1'-binaphthalene-2,2'-dicarboxylate in several steps. Enantiomeric alcohols were readily condensed with the chiral reagent in the presence of triethylamine under mild conditions. The diastereomeric esters formed from enantiomeric hydroxy acids were efficiently resolved by high-performance liquid chromatography on a normal phase column with n-pentane/ethyl acetate. These were highly responsive to a fluorescence detector (excitation wavelength 342 nm; emission wavelength 420 nm) with a detection limit of 200 pg.

KEYWORDS —— high-performance liquid chromatography; chiral derivatization reagent; chiral axis compound; acyl nitrile; fluorescence labeling; diastereomeric ester

In connection with pharmacokinetic studies of enantiomeric drugs a sensitive chiral derivatization reagent which is capable of forming diastereomers, is needed for the liquid chromatographic separation of enantiomers.[1-3] The derivatization reagents so far available for enantiomeric alcohols are unsatisfactory because of their lesser reactivity, and the insufficient sensitivity and resolution of the resulting diastereomers. In this communication we wish to report the development of new type of chiral derivatization reagents and their applicability to the resolution of enantiomeric hydroxy acids by high-performance liquid chromatography (HPLC).

The design of a promising derivatization reagent for the separation of enantiomeric alcohols by converting to the covalently bonded diastereomers requires the incorporation of suitable structural features, i.e. chirality leading to the efficient resolution, a function reactive toward the hydroxyl group, and a suitably intensive fluorophore. For this purpose an initial project was directed to the synthesis of the chiral axis compounds (+)- and (-)-2-methyl-1,1'-binaphthalene-2'-carbonyl nitriles.

Reduction of dimethyl 1,1'-binaphthalene-2,2'-dicarboxylate (I)[4] with LiAl(tert-BuO)$_3$H in benzene/ether afforded methyl 2-hydroxymethyl-1,1'-binaphthalene-2'-carboxylate (II), mp 118°C, which on treatment with 30% HBr in acetic acid was transformed into methyl 2-bromomethyl-1,1'-binaphthalene-2'-carboxylate (III), mp 138°C. Treatment of III with $NaBH_4$ in dimethylsulfoxide followed by alkaline hydrolysis gave (±)-2-methyl-1,1'-binaphthalene-2'-carboxylic acid (IVa) in 30%

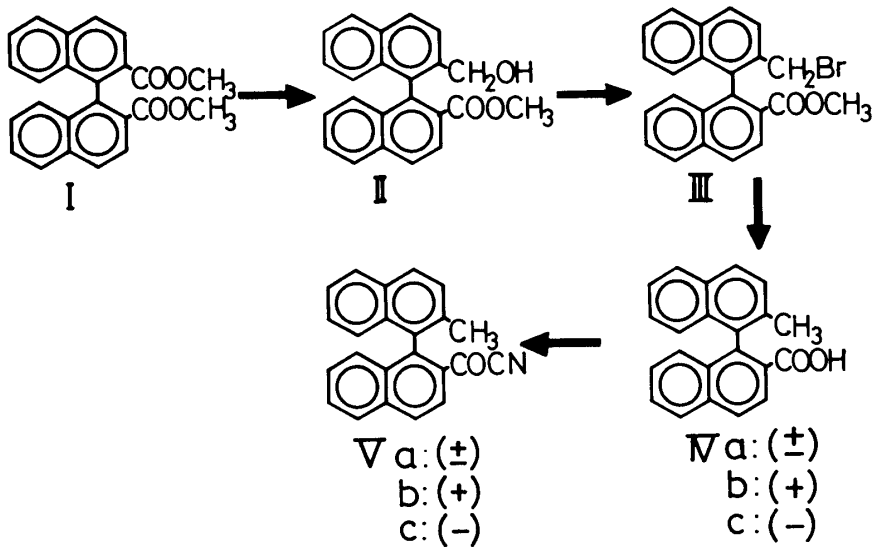

Chart 1

overall yield. mp 233°C. NMR ($CDCl_3$)δ: 1.96 (3H, s, $-CH_3$), 6.80-8.12 (12H, m, Ar-H). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.61; H, 5.13. Found: C, 84.32; H, 4.93. The optical resolution of IVa was accomplished by fractionally crystallizing the (-)-brucine salt from ethanol. This procedure was repeated several times to furnish the desired (+)-form (IVb), $[\alpha]_D^{20}$ +39.8° (c=0.93, $CHCl_3$) and (-)-form (IVc), $[\alpha]_D^{20}$ -41.3° (c=0.58, $CHCl_3$). When treated with oxalyl chloride in methylene chloride and then with trimethylsilyl cyanide in the presence of zinc iodide as a catalyst,[5,6] Va-c were readily transformed into (±)-, (+)-, and (-)-2-methyl-1,1'-binaphthalene-2'-carbonyl nitriles (Va-c), respectively. (±)-Form (Va): mp 110°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240 (C≡N), 1660 (C=O). NMR ($CDCl_3$)δ: 2.04 (3H, s, $-CH_3$), 6.72-8.24 (12H, s, Ar-H). MS m/z: 321 (M^+). Anal. Calcd for $C_{23}H_{15}NO$: C, 85.98; H, 4.67; N, 4.36. Found: C, 85.83; H, 4.73; N, 4.47. (+)-Form (Vb): $[\alpha]_D^{20}$ +35.8° (c=1.90, $CHCl_3$). (-)-Form (Vc): $[\alpha]_D^{20}$ -42.8° (c=1.05, $CHCl_3$). The optical purities of the two chiral reagents were both more than 99.0% as judged by the usual criteria.

The applicability of these derivatization reagents to the separation of enantiomeric alcohols by HPLC was then investigated. Quantitative coupling of alcohols with the reagent was effected at 60°C for 20 min in the presence of triethylamine, providing the diastereomeric esters. No racemization of the product or the derivatization reagent occurred, even under prolonged reaction conditions.

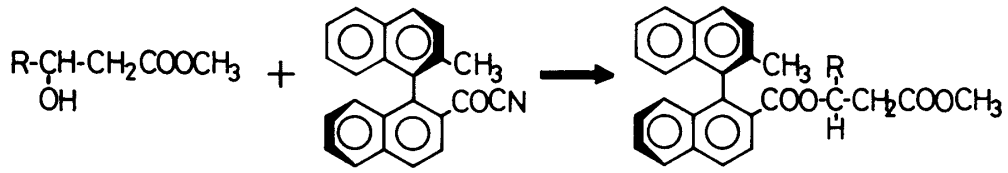

Chart 2

Table I. High-Performance Liquid Chromatographic Separation of Diastereomeric Esters Derived from Hydroxyl Compounds with (+)-2-Methyl-1,1'-binaphthalene-2'-carbonyl Nitrile

Compound	k'		α	R
Methyl 3-hydroxyoctanoate	7.83	9.25	1.18	3.09
Methyl 3-hydroxydecanoate	6.25	7.50	1.20	2.59
Methyl 3-hydroxylaurate	4.50	5.20	1.16	2.20
Methyl 3-hydroxystearate	3.67	4.25	1.16	1.89
Methyl mandelate	4.54	5.08	1.12	1.91

Condition: column, Cosmosil 5SL; mobile phase, n-pentane/ethyl acetate; flow rate, 1.0 ml/min.

The apparatus used was a Waters 6000A solvent delivery system equipped with a Hitachi Model 650-10LC fluorescence spectrophotometer. Each pair of the diastereomeric esters was resolved on a Cosmosil 5SL column when n-pentane/ethyl acetate was used as the mobile phase. The retention and resolution values of five pairs of diastereomers obtained with the reagent Vb are listed in Table I. The k', α, and R values refer to the capacity ratio, separation factor, and resolution factor for each pair of diastereomers. It is evident from the data that complete separation was accomplished for all the pairs of enantiomeric alcohols. The resulting ester was highly responsive to a fluorescence detector (excitation wavelength 342 nm; emission wavelength 420 nm) with a detection limit of 200 pg (S/N=10). On the other hand, the reagent itself exhibited no fluorescence.

These results show that newly developed reagents are of great use for the separation of trace amounts of enantiomeric alcohols by HPLC. Application of this method to the determination of enantiomeric drugs having an alcoholic hydroxyl group such as β-adrenergic blocking agents in biological fluids will be a subject in the future communication.

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