Chinese Chemical Letters Vol. 16, No. 11, pp 1471-1473, 2005 1471
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Enantioseparation of Racemic Anti-hepatitis New Drug Bicyclol with Crystallization

Wei HU, Yan LI, Chun Zhen ZHANG*

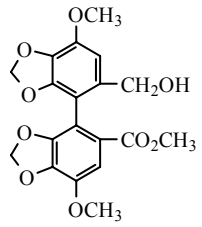
Institute of Materia Medica, Chinese Academy of Medical Sciences and
Peking Union Medical College, Beijing 100050

Abstract: The enantioseparation of anti-hepatitis new drug (±)-bicyclol was performed by optically active alkaloid. The alcoholic acid, the hydrolysate of bicyclol was reacted with optically active alkaloid, such as brucine, strychnine, quinidine *etc*., the diastereoisomeric salts were obtained by fractional recrystallization, then separately decomposed and esterified to obtain the two enantiomers of bicyclol. The pharmacological study showed that the effect of (-)-bicyclol was more potent than racemic bicyclol two times and the potency of (+)-bicyclol was incative.

Keywords: (±)-Bicyclol, 4, 4′-dimethoxy-2, 3, 2′, 3′-bis(methylenedioxy)-6-hydroxymethyl-6′-methoxy-carbonyl biphenyl, anti-hepatitis, resolution.

(±)-Bicyclol, 4, 4′-dimethoxy-2, 3, 2′, 3′-bis(methylenedioxy)-6-hydroxymethyl-6′-methoxy-carbonyl biphenyl is a new anti-hepatitis drug. The clinical study showed that bicyclol is a promising drug for chronic viral hepatitis B and C and it can markedly improve the clinical symptoms, such as elevated ALT (alanine aminotransferase) and AST (aspartate aminotransferase) in serum, and also in part of patients it returned positive HBeAg and HBV-DNA to negative. Bicyclol has been approved by State Food and Drug Administration of China and put to the market.

(±)-Bicyclol **1** is a multi-substituted biphenyl compound. There are substituents at 2,2', 6,6' positions, which prevent the single bond rotation between two benzene rings, so the two benzene rings are not located on the same plane and compose a pair of optically active atropisomers[1-3]. The X-ray analysis of single-crystal of bicyclol proved that the dihedral angle between the two benzene rings of (±)-bicyclol was 78.0 (1)[4]. The stable



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* E-mail: hw@imm.ac.cn

arrangement of molecules is held by the hydrogen bond intramolecular and Vander-Waals force under crystalline state, but not by intermolecular hydrogen bond. The X-ray analysis showed bicyclol in crystalline state existed as a racemic mixture. For investigation of the physiological activities of two isomers, the separation of isomers of (±)-bicyclol was carried out in our group.

Experimental

The separation procedure of (+)- and (-)-bicyclol was shown in **Scheme 1**. A mixture of 25 g (0.064 mol) (±)-bicyclol **1** and 10.8 g (0.19 mol) KOH in 200 mL water was stirred under reflux for 6 hours, then it was acidified with concentrated HCl to give 23 g of **2** in 95% yield. Compound **2** 10 g (0.027 mol) was mixed with 9 g (0.027 mol) quinidine in acetone for 1 hour, the solid was filtered and recrystallized from ethanol, 7.3 g (yield 78.4%) pure **3** was obtained, $[\alpha]_D^{17}$ +65.7, (c 0.56, $CHCl_3$), mp 230-231℃. The mother liquor was evaporated and recrystallized from ethanol, yielding 2.6 g (yield 28%) of **4**, $[\alpha]_D^{17}$ +106.6, (c 0.97, $CHCl_3$), mp 149-150℃. 2.5 g of **3** in 10 mL water was acidified with concentrated HCl, the solid was filtered and washed with water to give 1.02 g of (-)-**2** in 76% yield, $[\alpha]_D^{19}$ -37.1, (c 0.61, pyridine), mp 182-184℃. To a solution of 0.5 g (0.0013 mol) of (-)-**2** in 5 mL THF was added 10 mL diethylether solution of diazomethane which was obtained from 0.7 g of N-nitrose-N-methyl-N′-nitroguanidine in 50% aqueous potassium hydroxide solution. The mixture was stirred for 1 hour at room temperature, dried over anhydrous Na_2SO_4, after evaporation of solvent, 0.47 g of (-)-bicyclol (yield 91%) was obtained, $[\alpha]_D^{19}$ -41.8, (c 0.51, $CHCl_3$), mp 80-82℃, optical purity: 100%, (chiral column, Kromasil KR100-5CHI-DMB, mobile phase: isopropanol: *n*-hexane / 88:12), (**Figure 1 b**). ^{1}HNMR ($CDCl_3$, δ ppm) : 3.71 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.37 (dd, 2H, J=12, 17.7 Hz, CH_2OH), 5.91 (s, 2H, OCH_2O), 6.02 (d, 2H, J=6 Hz, OCH_2O), 7.26 (s, 1H, Ar-H), 7.33 (s, 1H, Ar-H). MS: *m/z* (%) 390 (M^+), 358 (-CHO), 329 (-CH_3), 314 (-CH_3), 299 (-CO). As the same procedure above, 1.6 g of **4** yielded 0.6 g (yield 70%) of (+)-**2**, $[\alpha]_D^{19}$ +37.7, (c 0.60, pyridine), mp 174-175℃. 0.36 g (0.00096 mol) of (+)-**2** yielded 0.32 g of (+)-bicyclol (yield 86%), $[\alpha]_D^{19}$ +40.2, (c 0.60, $CHCl_3$), mp 81-83℃, optical purity:100%, (chiral column, Kromasil KR100-5CHI-DMB, mobile phase: isopropanol: *n*-hexane / 88:12), (**Figure 1 c**). ^{1}HNMR ($CDCl_3$, δ ppm): 3.71 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.37 (dd, 2H, J=12, 17.8 Hz, CH_2OH), 5.91 (s, 2H, OCH_2O), 6.02 (d, 2H, J=6 Hz, OCH_2O), 7.26 (s, 1H, Ar-H), 7.33 (s, 1H, Ar-H). MS: *m/z* (%) 390 (M^+), 358 (-CHO), 329 (-CH_3), 314 (-CH_3), 299 (-CO).

Scheme 1

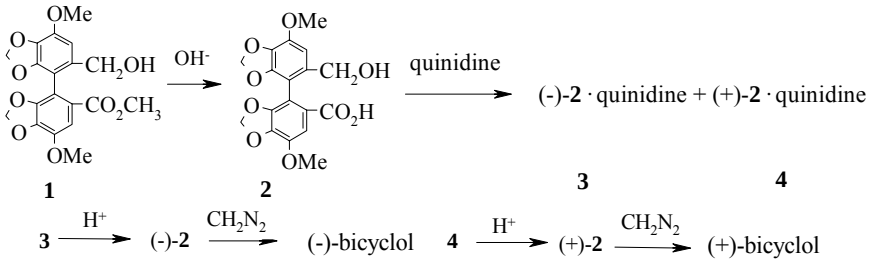
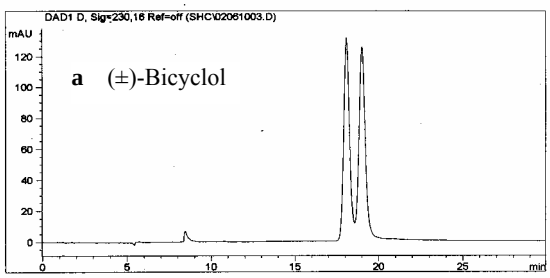
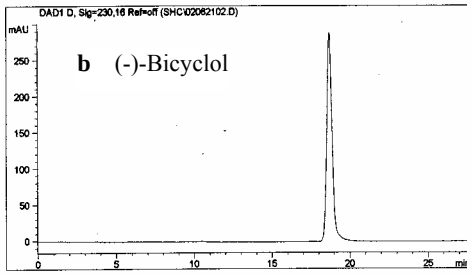


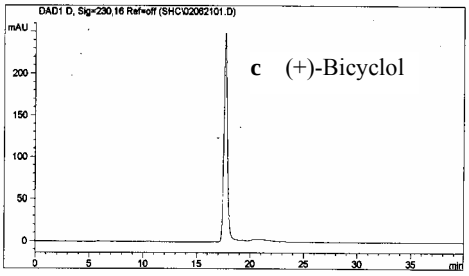
Figure 1 HPLC spectra of (±)-bicyclol, (-)-bicyclol and (+)-bicyclol



#	Time	Area	Area %	Width	Height
1	8.45	103.04	1.56	0.21	6.91
2	18.07	3181.95	48.07	0.38	131.06
3	18.99	3334.20	50.37	0.40	124.83
totals:		6619.19	100.00		262.80



#	Time	Area	Area %	Width	Height
1	17.55	14.48	0.20	0.43	0.57
2	18.67	7108.21	99.80	0.41	288.94
totals:		7122.69	100.00		289.51



#	Time	Area	Area %	Width	Height
1	17.66	5699.69	99.34	0.38	249.15
2	19.30	37.62	0.66	0.54	1.15
totals:		5737.30	100.00		250.31

The protective effect of (-)-bicyclol at dosage 100 mg/kg was similar to that of the racemic bicyclol at 200 mg/kg. The potency of (+)-bicyclol at 200 mg/kg was inactive.

References and Note

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3. H. M. Ho, L. Soo, H. S. Cheol, *et al.*, *Enantiomer*, **2001**, *5*(5), 313.
4. The test report of the X-ray analysis of single-crystal of bicyclol was deposited in the National Research Center for Analysis of Drugs and Metabolites.

Received 31 January, 2005