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Preparation of homochiral 9-anthryl-*tert*-butylcarbinol. The Configurational and Conformational NMR Study of its Carbamate Derivatives.

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Abstract: The homochiral carbamates of 9-anthryl-*tert*-butylcarbinol were prepared and their conformational equilibrium was studied. The absolute configuration was determined by comparison of the NMR data with MM calculations. The enantiomers of the alcohol were obtained after chromatographic separation of carbamate derivatives and their hydrolysis. The same homochiral alcohols were prepared by direct chiral column chromatography.

INTRODUCTION

In a recent study,[1] we reported the synthesis and a complete NMR study of 9-anthryl-*tert*-butylcarbinol (**1**), an interesting compound because of its high barrier to rotation around the C_9-C_{11} bond (22 Kcal/mol). In the present study we describe a new preparation of 9-anthryl-*tert*-butylcarbinol and the isolation of its two enantiomers (*R* and *S*) in two ways: by directly chromatographic separation on a chiral column or by diastereomeric derivation and posterior separation by standard chromatographic methods.

The preparation of chiral carbamates is a useful method for resolution of racemic mixtures. The reaction of homochiral isocyanates with racemic alcohols gives diastereomeric carbamates, which are easily separated by chromatography[2] and easily hydrolyzed to homochiral alcohols.

With the increasing interest of chiral chemistry,the latter method has been used extensively. However, there is a lack of structural studies of the intermediate compounds: the carbamates. There have been only few reports of slow rotation observed by NMR around the Carbonyl Carbon-Nitrogen bond in carbamates[3], none of which is related to the mono N-substituted. Here, a structural study of carbamate intermediates was carried out by DNMR and Molecular Mechanics calculations. We measured the energies associated with the rotation around the carbonyl carbon-nitrogen bond. The absolute configuration was determined by studying the influence of molecular geometry (distances between protons *peri* of anthracene ring and the phenyl ring) on chemical shifts.

RESULTS AND DISCUSSION

Racemic 9-anthryl-*tert*-butylcarbinol[1], a structural modification of Pirkle alcohol, is prepared by a new process based on the reduction of 1-(9-anthryl)-2,2-dimethyl-propanone obtained by reaction of the lithium derivative of 9-bromoanthracene with pivaloyl chloride, in a yield of 88% (Figure 1).

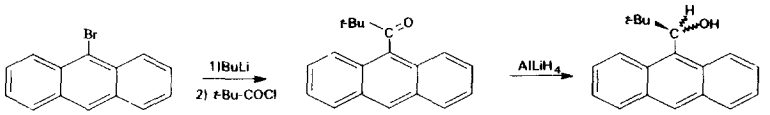

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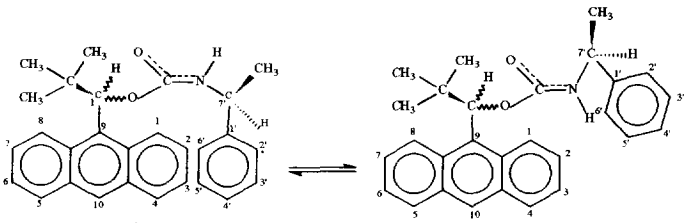
Figure 1.

The homochiral alcohol was prepared following Pirkle[4]. We obtained a mixture of two N-(1-phenylethyl)carbamates (**2a**) and (**2b**) (see Figure 2) derived from the reaction of racemic 9-anthryl-*tert*-butylcarbinol (**1**) with (*S*)-(-)-1-phenyl-ethyl-isocyanate (99%). The carbamates were separated by flash chromatography, giving diasteromeric (*R,S*) (**2a**) and (*S,S*) (**2b**), which are assigned as described below. The desired homochiral alcohols *R* ($[\alpha]_D^{20}$= 13; c= 0.9, $CHCl_3$) and *S* ($[\alpha]_D^{20}$= -14.5; c=1.1, $CHCl_3$) were then obtained by hydrolysis, (35 %yield).

The same values of optical activity were obtained for the compounds prepared by direct resolution of 9-anthryl-*tert*-butylcarbinol (**1**) by liquid chromatography using cellulosetriacetate (15-25 mm from Merck) as chiral stationary phase. Ethanol/water (96/4, 138 ml/h) was used as elution solvent in a column (200 × 25 mm) . The first enantiomer eluted with h'= 1 was (*S*); the second , with h'= 2.7 was (*R*) . Preparative runs were performed on 100 mg samples.

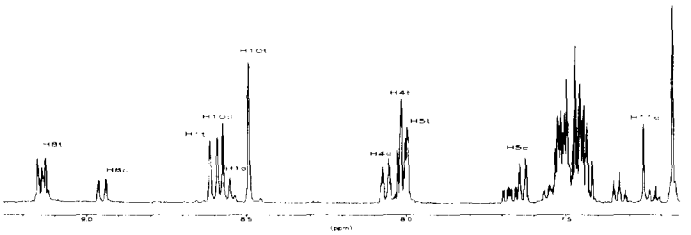


cisoid *transoid*

2a-(11*R*, 7'S)
2b-(11*S*, 7'*S*)

Figure 2.

^{1}H-NMR spectra of urethane derivatives show, at room temperature, a slow rotation around the amide bond (Figure 2). At 250 K the spectrum of each carbamate shows an equilibrium between two rotamers (*cisoid* and *transoid*) in an unequal proportion (25/75 for **2a,** (Spectrum 1) and 10/90 for **2b**) which indicates a difference in their relative stability.



Spectrum 1: Part of NMR spectrum of **2a** at 250 K in CD_3COCD_3

Molecular mechanics calculations (MacroModel[5] with MM3*[6] and OPLS[7] force fields) for each carbamate revealed that the rotamer of lower energy is *transoid* for the *R,S* and *cisoid* for the *S,S* isomer (Table 3). These results allowed us to assign rotamers for each diastereomer, **2a** and **2b**, (Table 1), although experimental energy differences between rotamers deduced from integrated NMR spectra (Table 1) do not quantitatively agree with the MM- calculated energy differences (Table 3).

compound	*% (250K)*	ΔG^o*/(kcal·mol^{-1})*	T_c*/(K)*	*k/(s^{-1})*	$\Delta G^{\neq}$*/(kcal·mol^{-1})*
cisoid	25				
2a-*RS*		-0.54	309	115	15.19
transoid	75				
cisoid	90				
2b-*SS*		1.09	296	115	14.52
transoid	10				

Table 1.

The ^{1}H-NMR spectra assigned for each rotamer of the diastereomeric carbamates at 250 K are given in Table 2.

proton	*2a cisoid*	*2a transoid*	*2b cisoid*	*2b transoid*
H_1	8.56	8.60	8.59	8.59
H_2	—	7.54	7.55	—
H_3	—	7.52	7.45	—
H_4	8.06	8.02	8.07	8.01
H_5	7.57	8.00	8.04	7.90
H_6	—	7.48	7.35	—
H_7	7.65	7.44	7.42	—
H_8	8.95	9.14	9.07	8.23
H_{10}	8.55	8.49	8.56	8.46
H_{11}	7.22	7.14	7.14	7.07
$H_{2'}$=$H_{6'}$	—	7.07	7.45	—
$H_{3'}$=$H_{7'}$	—	6.97	7.36	—
$H_{4'}$	—	6.97	7.23	—
$H_{7'}$	4.94	4.7	4.60	5.20
CH_3	1.33	1.34	1.26	1.51
t-Bu	0.63	1.04	0.96	1.00

Table 2: ^1H NMR assignment of **2a** and **2b** at 250K in CD_3COCD_3.

Unambiguous assignment methods used include ^1H-^1H correlated 2D techniques and homonuclear $^1H\{^1H\}$ NOE measurements. Moreover, in these last experiments the saturation transfer observed permitted us to correlate the signals of the two rotamers for each carbamate. In **2b,** we assigned H_1 (8.59) and H_8 (8.23) of rotamer *transoid* after irradiation of H_1 (8.59) and H_8 (9.07) of rotamer *cisoid* respectively. By analogy, in **2a** we assigned H_1 (8.56) and H_8 (8.95) of rotamer *cisoid* after irradiation of H_1 (8.60) and H_8 (9.14) of rotamer *transoid* respectively.

At high temperatures all resonances broaden owing to an increasing rate of conformational exchange and finally achieve coalescence. Coalescence temperatures for H_{10} are shown in Table 1. Rate constants (k) were determined for each compound by a Complete ^1H DNMR Line Shape Analysis[8] (CLSA) performed on the temperature dependence of resonances of H_{10} , and $\Delta G^{\neq}$ values were calculated using the Eyring equation (Table 1). These values are consistent with calculated barriers for carbamates rotation[9].

The calculated distances between H_1 and $C_{1'}$ and H_8 and $C_{1'}$ are shown in Table 3. According to these values the mean influence of anisotropy due to the phenyl ring is on H_8. The distance values between H_1 and $C_{1'}$ are very similar, for all the compounds studied, which explains the similar chemical shift of H_1 in the second carbamate eluted (8.56 and 8.60) and an equal chemical shift in the first (8.59). The distance values between H_8 and $C_{1'}$ are very similar in one of the diastereoisomers (*R,S*). This is reflected, as before, in the similarity of H_8 chemical shift (8.95 and 9.14) of the second carbamate eluted, which could therefore be assigned to **2a,** described above. However, the distance values between H_8 and $C_{1'}$ are markedly different in the other diastereoisomer (*S,S*), which explains the different chemical for H_8 in each rotamer (8.23 and 9.07) of first carbamate eluted which in this case corresponds to **2b**. On the basis of these results, we can assume that the absolute configuration of (-)-9-anthryl-*tert*-butylcarbinol derived from the first carbamate eluted is *S* and, by analogy, the absolute configuration of (+)-9-anthryl-*tert*-butylcarbinol is *R* .

MM3*	*E/(Kcal.mol^{-1})*	*d(H_{11}-H_1) /(A°)*	*d(H_{11}-H_8) /(A°)*	*d(H_1-$C_{1'}$)/ (A°)*	*d(H_8-$C_{1'}$) /(A°)*
2a-RS cisoid	112.0	1.831	3.741	6.897	3.659
2a-RS transoid	108.3	1.840	3.750	6.852	4.632
2b-SS cisoid	110.6	1.827	3.742	7.070	3.023
2b-SS transoid	113.7	1.832	3.745	6.692	5.794

OPLS	*E/(Kcal.mol^{-1})*	*d(H_{11}-H_1) /(A°)*	*d(H_{11}-H_8) /(A°)*	*d(H_1-$C_{1'}$) /(A°)*	*d(H_8-$C_{1'}$)/(A°)*
2a-RS cisoid	-53.3	1.991	3.735	6.680	4.073
2a-RS transoid	-60.6	1.982	3.727	5.359	4.933
2b-SS cisoid	-57.1	1.990	3.727	7.032	3.071
2b-SS transoid	-50.1	1.989	3.731	6.796	5.897

Table 3: Calculated distances by MM.

EXPERIMENTAL

Synthesis: 1-(9-anthryl)-2,2-dimethylpropanone[10]: A solution (1.6 M) of butyllithium (9.5 mL, 15.18 mmol) was slowly added to a diethyl oxide (60 mL) solution of 9-bromoanthracene (3g, 11.68 mmol) kept under N_2 under continuous stirring The reaction was completed after 3h, the mixture was cooled to 233 K, pivaloyl chloride (1.9 mL, 15.18 mmol) was added dropwise and the temperature was kept at 253 K. After 2h the reaction was quenched, and the organic layer was separated, dried and concentrated. The solid residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 95/5 v/v). : mp. 138-140°C; IR (KBr) 3058, 2973, 2868, 1686 (C=0), 1475,1075,906 and 737 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.32(s, 9H), 7.99 (m, 2H), 7.75 (m, 2H) and 7.26 (m, 4H) , ^{13}C-NMR ($CDCl_3$) : 28.06, 46.04, 125.3, 125.5, 126.0, 127.2, 127.4, 128.7, 130.9, 136.4 and 218.2.

9-anthryl-*tert*-butylcarbinol (1): A diethyl oxide solution (20 mL) of $AlLiH_4$ (56 mg, 1.476 mmol) was slowly added to a diethyl oxide (20 mL) solution of 1-(9-anthryl)-2,2-dimethylpropanone (250 mg, 0.954 mmol) kept under N_2. Reduction was completed in 20 min.. After adding 5 mL of HCl (1N) the organic layer was separated, dried and concentrated. The solid residue was purified (92% yield) by recrystallization in cyclohexane.

N-(1-phenylethyl)carbamates (2a and **2b)**: Carbamates were prepared according to the literature[4]: racemic 9-anthryl-*tert*-butyl-carbinol (180 mg, 0.68 mmol) and (*S*)-(-)-(1-phenylethyl)isocyanate 99% (10.98 ml, 0.68 mmol) were mixed and heated to 80°C while protected by a drying tube for 72 hr. The mixture was then chromatographed with toluene/methylene chloride (2/1) on a 2.5×20 cm column of silica-gel.The first major fraction to be eluted was (*S,S*)-(+)-(**2a**) (130 mg; 0.34 mmol, 93%). Recrystallization from hexane gave white needles: mp 145-147°C; IR (KBr): 3324 (NH), 1688, 1532, 1253, 1074, 1004, 801, 760, and 737 cm^{-1}; $[\alpha]_D^{20}$= 27.9 ±2.1 (c: 0.9, chloroform).The second major fraction to be eluted was (*R,S*)-(-)-(**2b**) (110 mg; 0.27mmol, 78%). Recrystallization from hexane gave white needles: mp 117-119°C; IR (KBr): 3310 (NH), 1691, 1527, 1082, 1005 and 757 cm^{-1}; $[\alpha]_D^{20}$= -92.3±1.6 (c= 1.26, chloroform).

Enantiomeric carbamates: (*R,R*)-(-), $[\alpha]_D^{20}$= -29.1±1.8 (c= 1.1, chloroform) and (*S,R*)-(+), $[\alpha]_D^{20}$= 93.6 ±1.2 (c= 1.0, chloroform) were obtained by an analogous reaction using (*R*)-(+)-(1-phenylethyl)-isocyanate 99%.

NMR experiments: NMR experiments at variable temperature were conducted on a Bruker AC400 spectrometer with a 5-mm QNP probe and using CD_3COCD_3 as the solvent. The operating frequency was 400.16 MHz for ^{1}H.The temperature of the probe was calibrated by the methanol standard method, and a delay of 600s was applied before recording the NMR spectra at each new temperature. All the NOE experiments were recorded using sealed sample tubes from which the dissolved oxygen had been first removed by the freeeze-thaw technique. NOE difference spectra were obtained using 8 s of low-power (typically 48L) presaturation; two dummy scans were used.

MM calculations: MM calculations were carried out on a SGI workstation using the Macromodel program with two of the force fields implemented in it : MM3* and OPLS. The minimization used was PRCG[11] (PR conjugate gradient).

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