The Structure of Fortesol, a Novel Fused Tricyclic Alcohol Used for Resolution of Phosphinic and Carboxylic Acids

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Introduction

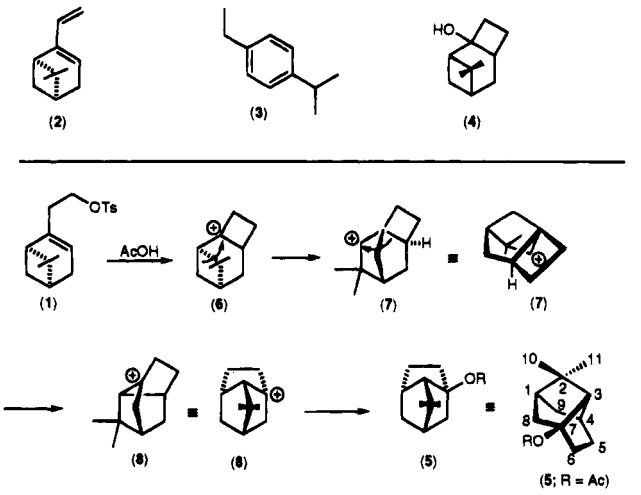
On solvolysis in aqueous ethanol, the *p*-toluenesulfonate of nopol (**1**; Scheme 1) has been reported[1] to yield nopadiene (**2**; 31%), 1-ethyl-4-isopropylbenzene (**3**; 6%), and a previously unknown alcohol (**4**; 41%). In acetic acid containing sodium acetate the yield of the acetate of the new alcohol rose to 91%. Although a tertiary alcohol, this product of rearrangement of nopol was remarkably stable to acid and could be purified through its prolonged refluxing in strong sulfuric acid which acted by decomposing all the minor impurities and leaving the new alcohol unaffected. Structure **4** was assigned on the basis of chemical degradative methods, mainly oxidation with lead tetraacetate which gave products believed to be exclusive to a cyclobutanol.[2,3] The earlier 220 MHz ^{1}H-NMR spectrum of the new alcohol proved too complex to confirm the structure and even recent 400 MHz spectra did not provide an unequivocal answer. Our present work has provided a novel structure (**5**; R = H) for the tertiary alcohol.

In recent research on the resolution of racemic phosphinic acids, we sought an enantiomerically advantageous replacement for the more commonly used[4,5] menthyl or bornyl esters. Phosphinate esters of the new alcohol obtained by solvolysis of nopyl tosylate proved to be superior to the menthyl or bornyl esters in giving a greater excess of one enantiomer and easier separation of the two enantiomers. The resistance of the alcohol to acid and to heat and its simple preparation on a large scale makes it convenient to work with. In this Note, results are described of a new structure determination of the alcohol derived from nopol. To save confusion with complex nomenclature, this new structure has been called fortesol. There is a brief description of the use of fortesol as a novel chiral resolving agent for racemic carboxylic and phosphinic acids.

Experimental Section

Preparation of Fortesol.[6] Fortesyl acetate was prepared by acetolysis[1] of the *p*-toluenesulfonate of commercially available (−)-nopol (Aldrich) and was then reduced with $LiAlH_4$ to give fortesol, mp 70–74 °C (from Et_2O; lit.,[1] 75–77 °C); $[\alpha]^{20}_D = -48°$ (c = 5; EtOH); MS (EI; $M^{+\cdot}$) m/z 166; ^{1}H-NMR is given in Table 1.

Scheme 1



Chiral Resolution of Racemic Acids Using Fortesol.[6] **(a) Preparation of Fortesyl 2-Phenylpropionate.** To 2-phenylpropionic acid (0.6 g, 3.99 mmol) was added thionyl chloride (25 mL) and the mixture was refluxed for 1.5 h. Excess of thionyl chloride was evaporated off under reduced pressure and the residual acid chloride was used in the next stage of preparation without purification. To a stirred mixture of optically active Fortesol (0.68 g, 4.1 mmol) and DMAP (0.5 g, 4.1 mmol) in anhydrous diethyl ether (15 mL) was added a solution of the 2-phenylpropionyl chloride in anhydrous diethyl ether (5 mL) over a period of 5 min at 0 °C. The mixture was stirred at rt for 16 h. The resulting amine hydrochloride was filtered off and the filtrate was washed with aqueous Na_2CO_3 and HCl (1 M) and then dried ($MgSO_4$). Evaporation of the solvent gave the crude ester as an oil (0.76 g, 65% yield) which was left at about 0 °C for 2 d. The resulting oily crystals were recrystallized by dissolving them in petroleum ether (bp 60–80 °C) and keeping the solution at −20 °C for 2 d. Two similar recrystallizations gave an enantiomer, mp 66–68 °C, for which the structure was obtained by X-ray analysis (**5**; R = 2-phenylpropionyl): MS (FAB, 3-NOBA) $[M + H]^+$, m/z 299; ^{1}H-NMR (200 MHz, $CDCl_3$), δ = 0.68 (s, 3H), 0.70 (dd, 1H), 0.92 (s, 3H), 1.47 (d, 3H), 1.35–2.5 (m, 10H), 3.61 (q, 1H), 7.28 (m, 5H); IR (CH_2Cl_2), 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.7. Found: C, 80.0; H, 8.7%.

(b) Preparation of Fortesyl Methylphenylphosphinate. Fortesol (1.77 g; 10.67 mmol) and DMAP (1.28 g; 10.46 mmol) in dry Et_2O (15 mL) were added to a solution of methylphenylphosphinyl chloride (1.68 g; 9.36 mmol) in dry Et_2O (5 mL) over a period of 5 min at 0 °C. The mixture was stirred for 16 h at rt and was then filtered. Evaporation of the solvent from the filtrate gave an oil (3.07 g; 94% yield) in an enantiomer ratio of about 3:1 (^{1}H-NMR) which was separated by chromatography on a column (65 × 200 mm) of silica gel, using EtOAc as eluant. One enantiomer (1.49 g) was readily isolated as an oil: $[\alpha]^{25}_D$ = 23.5° (c = 0.61; CH_2Cl_2); MS (EI; $M^{+\cdot}$), m/z 304; ^{1}H-NMR (200 MHz, $CDCl_3$), δ = 0.68 (d, 1H), 1.0 (s, 3H), 1.2 (s, 3H), 1.2–2.58 (m, 10H), 1.60 (d, 3H), 7.52 (m, 3H), 7.80 (m, 2H). Anal. Calcd for $C_{18}H_{22}O_2P$: C, 71.1; H, 8.2. Found: C, 71.0; H, 8.4%.

Results and Discussion

It was found that consistent ^{1}H-NMR spectroscopic assignments of shifts and couplings could not be made if the structures of the carboxylic and phosphinic acid esters of the rearrangement product of nopol were based on structure **4**. Indeed, the spectrum of the alcohol itself was not interpretable in terms of structure **4**. Because

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Table 1. Assignments of ^1H and ^{13}C Resonances in NMR Spectra of Forestol (5; R = H) in $CDCl_3$ as Solvent[a]

carbon atom (δ)	1 (44.8), 2 (48.8), 3 (60.1), 4 (38.2), 5 (27.7), 6 (41.3), 7 (85.9), 8 (49.5), 9 (38.8), 10 (23.5), 11 (21.3)
hydrogen atom (δ)	1 eq (1.60, m), 3 eq (1.62, m), 4 eq (2.36, m), 5 eq (1.35, m), 5 ax (1.88, m), 6 eq (2.05, m), 6 ax (1.83, m), 8 eq (2.25, m), 8 ax (1.40, m), 9 eq (2.14, m), 9 ax (0.71, m), 10 (1.21, s, 3H), 11 (0.98, s, 3H)

[a] The carbon atoms are numbered as in structure **5**. The hydrogen atoms carry the same numbers as the carbons to which they are attached. The shift for the OH proton is concentration dependent.

of these difficulties, an X-ray structure determination[7] was made on the 2-phenylpropionate of the new alcohol and this clearly showed that its true structure was 2,2-dimethyltricyclo[4,2,1,$0^{3,7}$]nonan-7-ol (**5**; R = H). The structure of fortesol, having three fused five-membered rings, appears to be a novel ring combination, although it is similar to a known tricyclic system having a fused six- and two five-membered rings.[8] The structure **5** with the two-carbon bridge is believed to be unique. With this structure, ^1H nuclear magnetic resonances could be assigned, though with some difficulty because of overlapping or very close hydrogen shifts which were not readily resolved even at 400 MHz. Through a combination of two dimensional cross-coupling ($^1H-^1H$ and $^1H-^{13}C$), NOE results, off-resonance decoupling, examination of the acetate and 3,5-dinitrobenzoate esters, shift reagents and solvent shifts, and finally, application of the PANIC[9] program, assignments for all hydrogens and carbons in fortesol were arrived at and are shown in Table 1. It is notable that, as with many similar structures containing multifused rings,[10] there is one axial proton which is shifted well upfield, to δ 0.71 in this case.

A probable mechanism of formation of fortesol from nopyl tosylate is shown in Scheme 1. The first step is to form a second cyclobutane ring (**6**) by cyclization of the side chain of the tosylate onto the main ring with synchronous loss of the tosyl group; this is similar to the known mechanism of cyclization of tosylates of β,γ-alkenyl alcohols.[11] The next step, expansion of the original cyclobutane ring, would be a rearrangement similar to that reported for several related molecules in which a six-membered ring was fused to a pinane skeleton.[12-15] For these last synthetic model systems, in which a fused pinane derivative was isolated, the fused ring was on the side of the molecule *away* from the *gem*-dimethyl bridge. There is no reason to think that the nopol/fortesol system, in which steric effects would be of greater importance than in the model structures, would behave differently.

The situation in structure **6**, in which the newly formed cyclobutane ring is orientated away from the *gem*-dimethyl bridge, might be thought to favor migration of that bridge rather than the methylene one. However, consideration of the stereochemistry of the product shows that this is not the case. The bridgehead ring junction with the newly formed cyclobutane ring in structure **7** is fixed, so that the other ring junction must be in the *exo*-position; a ring junction in the endo-position would produce an impossibly strained molecule. Thus, the hydrogen atom shown in structure **6** must be on the opposite side of the molecule to the migrating bridge. This hydrogen atom controls the rearrangement pathways open to structure **6**, permitting only a shift of the methylene bridge to yield structure **7**. Simple bond migration then gives **8**. A similar shift of the *gem*-dimethyl bridge can only result in the reopening of the fused cyclobutane ring to give product **3** because the pinane ring is also opened.[16] Other possible pathways from nopol to fortesol involve loss of chirality through formation of symmetrical intermediates or would need to invoke the intervention of nonclassical carbocations. Labeling experiments are in hand to help determine the mechanism of the rearrangement.

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