Synthesis of Optically Active 5,6,7,8-Tetrahydroquinolines

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(+)-*(R)*-5-Methyl- and (+)-*(R)*-2,5-dimethyl-8-isopropylidene-5,6-dihydro-7*H*-quinoline, **7** and **11**, were synthesized by reaction of *(R)*-pulegon morpholino-enamine with acrolein or methyl vinyl ketone. The Michael adducts thus formed were reacted with hydroxylammonium hydrochloride in polar media. Compound **7** was also obtained by thermal rearrangement of the *O*-allyl ether of pulegone oxime. The selectivity of both synthetic methods were rather poor (30-49%). Isolation of **7** and **11** in the pure state was accomplished by preparative glc.

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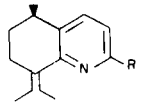
In connection with our interest in the synthesis and in the study of the chiroptical properties of optically active pyridines [1,2], we needed compounds in which the heterocyclic ring is fused with an alicyclic moiety bearing only a chirality center. Such pyridine derivatives can be available, in principle, from commercial (+)-*(R)*-pulegone, a very popular member of the "chiral pool". This natural product resulted in a very useful starting material for the synthesis of (+)-actinidine [3], which has a cyclopentene ring fused with a pyridine ring.

In this paper we report the results obtained in the transformation of (+)-*(R)*-pulegone into cyclohexa[1,2-*b*]pyridines having the general formula:

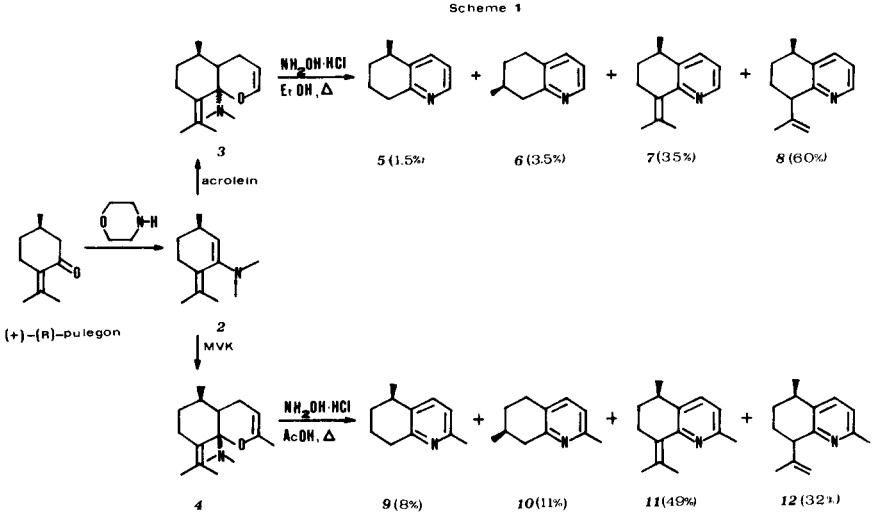


R = H
R = CH_3

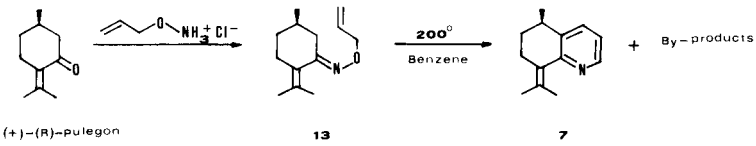
The reaction scheme chosen to effect this conversion is depicted in Scheme 1. In the first step the starting chiral compound was converted into the corresponding morpholino-enamine **2**. Other types of enamines, as those formed from piperidine or pyrrolidine, were less efficient, in fact, although the formation of **2** from (+)-*(R)*-pulegone requires longer reaction time than in the case of piperidine and pyrrolidine, higher yields in the following cycloaddition step both with acrolein and methyl vinyl ketone (MVK) were achieved. Compound **2** obtained in about 50% yield resulted isomerically pure by nmr analysis. However, variable amounts (5-15%) of the two possible morpholino-enamines of 3-methylcyclohexanone were also found in the reaction mixture. These compounds were identified by glc and ms analysis and derived very likely from 3-methylcyclohexanone formed in turn by a well known acid-catalyzed retroaldolization reaction on (+)-*(R)*-pulegone [4].

Compound **2** was reacted with acrolein or MVK; the resulting cycloaddition products were not isolated and used without any purification in the following treatment with hydroxylamine hydrochloride in polar solvents. In both cases the selectivity of the cyclization reaction was rather poor. Very different yields in pyridine derivatives were obtained depending on the structure of the enamine/unsatu-

Scheme 1



Scheme 2



rated carbonyl compound adduct and on the reaction conditions of the cyclization step: i) the cyclization of **3** in hydrochloric acid solution produced the tetrahydroquinoline derivatives **5, 6, 7** and **8** in only an 8% yield; ii) the total yield in **9, 10, 11** and **12** was much higher (40%) for the pulegone-enamine/MVK adduct **4** in acetic acid than for the adduct with acrolein under the same reaction conditions ($\leq$3-4%); iii) the cyclization of **4** in hydrochloric acid solution never gave yields higher than 15%.

As for the reaction products derived from **3** (Scheme 1), glc analysis showed the presence of four components; among these only the major one was formed in sufficient amount to be isolated by preparative glc. It was identified by nmr and ms analysis as 5-methyl-8-(2-propenyl)-5,6,7,8-tetrahydroquinoline (**8**), occurring very probably as a diastereomeric mixture. The desired pyridine **7** accounted only for 35% of the reaction products (Scheme 1). Its structure was determined by comparison of mass spectrum and glc-retention times with those of an authentic sample obtained by the alternative synthetic route described below (Scheme 2).

The minor components were 5-methyl- (**5**) and 7-methyl-5,6,7,8-tetrahydroquinoline (**6**) in about 30:70 molar ratio (glc). These compounds derive from 3-methylcyclohexanone morpholino-enamine formed simultaneously with the pulegone-enamine. The structure of these two isomers, which we were not able to separate in the pure state through chromatographic techniques, was confirmed as follows: a commercial sample of 7-methylquinoline containing about 25% of the 5-methyl substituted isomer underwent selective hydrogenation at the benzene ring in the presence of catalytic amount of Pt Adams in trifluoroacetic acid [5]. The mixture of 7-methyl- and 5-methyl-5,6,7,8-tetrahydroquinoline thus obtained was submitted to glc and ms analysis: the comparison between the analytical data showed that 7-methyl-5,6,7,8-tetrahydroquinoline (**6**) was the major component also among the products of the cyclization of **3** (Scheme 1).

Analogously, the reaction of **4** with hydroxylamine hydrochloride in acetic acid gave a mixture of four products (glc) (Scheme 1). In this case the desired pyridine **11** was the main component (49%). We were able to isolate compounds **11** and **12** in the pure state by preparative glc and to confirm their identity by nmr and ms spectroscopy. Also in this case it was impossible to effect any separation of the two isomeric dimethyltetrahydroquinolines **9** and **10** (about 40:60 molar ratio by glc); their structures were determined on the basis of the nmr data obtained for the mixture of **5** and **6**.

Recently a new interesting synthesis of 5,6,7,8-tetrahydroquinolines was published by two different research groups [6,7]. It consists in a one-step thermal conversion of cyclohexanone *O*-allyloximes into tetrahydroquinoline derivatives in 30-60% yields through a [2,3] sigmatropic rearrangement. Thus heating at 200° a benzene solution of **13** (Scheme 2) in a sealed tube gave **7** with about 30% selectivity. From this reaction mixture, **7** was isolated in 15% yield by preparative glc. In this case only *(R)*-pulegone (11%), 3-methylcyclohexanone (13%) and a small amount ($\leq$2%) of **5** and **6** were recognized by means of glc and ms analysis among many other by-products ($\sim$44%).

We have not determined the relationship between rotatory power and optical purity of the chiral 5,6,7,8-tetrahydroquinolines we prepared, however, we can reasonably assume for **7** and **11** the same minimum optical purity of the starting *(R)*-pulegone ($\sim$95%) [8]. In fact, we believe that the reaction sequences employed for the preparation of **7** and **11** (Schemes 1 and 2) are racemization free on the basis of the mechanisms known or proposed for the various steps of their synthesis. Therefore the maximum rotatory power of **7** and **11** in chloroform resulted to be $[\alpha]_D^{25}$ +67.4 and $[\alpha]_D^{25}$ +17.2 respectively.

Although the preparative routes to **7** and **11** are not experimentally expeditous, to our knowledge no alternative methods exist in the literature leading to these compounds.

The synthesis of other more convenient chiral 5,6,7,8-tetrahydroquinolines with similar structure starting from other cheap optically active terpenic compounds are currently in progress in our laboratories.

EXPERIMENTAL

Boiling points are uncorrected. The glc analyses were performed on a Perkin-Elmer 3920-B gas chromatograph, using the columns and the temperatures specified. The products were separated by use of a Perkin-Elmer F-21 preparative scale gas chromatograph under the conditions and at the temperatures specified. The nmr spectra at 60 MHz were obtained with a Varian T-60 spectrometer and at 90 MHz with a Bruker WH-90 spectrometer in deuteriochloroform solutions using tetramethylsilane as an internal standard (δ = 0). Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6L mass spectrometer operating at 70 eV. The optical rotations were taken on a Perkin-Elmer 241 polarimeter in 1 dm tubes. Elemental analyses were performed by Perkin-Elmer Elemental Analyzer Model 240-B.

Materials.

(+)-*(R)*-Pulegon ($[\alpha]_{546}^{20}$ +30) and 7-methylquinoline were commercial products (Fluka AG). *O*-Allylhydroxylamine hydrochloride was obtained according to the method described by Cope, *et al.* [9].

(+)-*(R)*-Pulegon Morpholino-enamine (**2**).

(+)-*(R)*-Pulegon, 15.1 g (0.1 mole), morpholine, 25.8 g (0.3 mole) and *p*-toluenesulfonic acid, 1.0 g (5 mmoles) in 300 ml of anhydrous toluene were refluxed in a Kumagawa apparatus in the presence of 40 g of 4A molecular sieves. After ten days the mixture was neutralized with potassium carbonate, the solvent was evaporated and the crude residue distilled *in vacuo* to give **2**, 95% pure by glc (2 m × 2 mm column packed with 5% SE-30 on Chromosorb W and heated at 160°), 9.27 g (49% yield), bp 75° (0.2 mm Hg); ms: m/e (%), 206 (100), 221 (M^+, 26.8), 207 (17), 41 (15.3), 77 (12.6), 81 (12.5), 163 (10.9), 179 (9.8), 149 (9.8), 79 (9.8); nmr: (δ ppm), 4.50 (H, d), 3.73-3.40 (4H, m), 2.80-2.53 (4H, m), 2.00 (3H, s), 1.72 (3H, s), 0.98 (3H, d). The glc-ms analysis (glc conditions were the same reported previously) of the crude reaction mixture showed the presence of a component (13%) having M^+ 181 corresponding to the molecular weight of the two possible enamines resulting from 3-methylcyclohexanone, 1-morpholino-3-methyl- and 1-morpholino-5-methylcyclohexanone.

(+)-*(R)*-5-Methyl-8-isopropylidene-5,6-dihydro-7*H*-quinoline (**7**).

a) *via* *O*-Allyl Ether of Pulegone Oxime.

(+)-*(R)*-Pulegon, 3.75 g (24.7 mmoles), *O*-allylhydroxylamine hydrochloride, 2.7 g (25 mmoles) and pyridine, 11 ml, were stirred for 40 hours at room temperature. The mixture was acidified with 10% hydrochloric acid and extracted twice with ether (2 × 10 ml). The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 4.6 g of crude *O*-allyl ether of pulegone oxime, which was dissolved in dry benzene (20 ml) and heated at 200° in a sealed tube for 40 hours. The glc analysis (2 m × 2 mm column packed with 15% Carbowax 20M on Chromosorb W and heated at 190°) of the crude reaction mixture showed the following composition: 30% of **7**, 13% of 3-methylcyclohexanone, 11% of pulegone and 2% of 5-methyl- and 7-methyl-5,6,7,8-tetrahydroquinoline. The remaining 44% was a complex mixture of fifteen by-products, which were present in low amounts and were not identified. The reaction mixture was stirred with 10% hydrochloric acid (10 ml), the aqueous layer was separated, made strongly alkaline with sodium hydroxide and extracted twice with ether (2 × 15 ml). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The remaining brown oil was distilled bulb-to-bulb, bp 110-130° (5 mm Hg), affording 0.89 g of basic products from which only the major one (57%) was recovered in the pure state by preparative glc (2 m × 7 mm column packed with 5% Carbowax 1500 on Chromosorb W 70-80 mesh and heated at 150°). It was identified by ms and nmr analysis as 5-methyl-8-isopropylidene-5,6-dihydro-7*H*-quinoline (**7**); ms: m/e (%), 187 (M^+, 100), 172 (75), 186 (52.5), 130 (45), 144 (42.5), 146 (32.5), 158 (22), 159 (21), 131 (18), 166 (17); nmr: (δ ppm) 8.48-8.28 (αH, m), 7.53-7.30 (γH, m), 7.10-6.85 (βH, m), 2.13 (3H, d), 1.85 (3H, s), 1.25 (3H, d); $[\alpha]_D^{25}$ +61.15 (*c* 3.14, chloroform).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.3; H, 9.0; N, 7.5.

b) *via* Morpholino-enamine.

(+)-*(R)*-Pulegon morpholino-enamine (**2**), 7.0 g (32 mmoles) and acrolein, 2.0 g (36 mmoles), were refluxed for 60 hours in anhydrous benzene (25 ml). After evaporation of the solvent the residue was kept in ethanol (33 ml) and an aqueous solution of hydroxylammonium hydrochloride, 6.14 g (88 mmoles) in 33 ml of water, was added. The mixture was refluxed for 4 hours in the presence of a few drops of hydrochloric acid, under nitrogen atmosphere. After cooling the mixture was diluted with water (100 ml) and neutralized with sodium carbonate. Extraction with ether, drying over sodium sulfate and bulb-to-bulb distillation afforded 0.68 g of a yellow oil, bp 145-150° (25 mm Hg). The glc-ms analysis (2 m × 2 mm column packed with 15% Carbowax 20M on Chromosorb W and heated at 190°) showed the following composition of the distillate: 60% of 5-methyl-8-(2-propenyl)-5,6,7,8-tetrahydroquinoline (**8**), 35% of **7**, 3.5% of **6** [10] and 1.5% of **5** [7]. Compound **7** was identified by comparison of mass spectrum and glc-retention times (glc-analysis conditions were the same reported above) with those of an authentic sample obtained by the previously described route.

Compound **8** was isolated in the pure state by preparative glc (2 m × 7 mm column packed with 5% Carbowax 1500 on Chromosorb W 70-80 mesh and heated at 150°); ms: m/e (%), 159 (100), 158 (46), 156 (26), 130 (26), 142 (23.5), 144 (23), 187 (M^+, 22.5), 160 (14), 131 (17.5), 146 (11.5); nmr: (δ ppm) 8.46-8.26 (αH, m), 7.56-7.30 (γH, m), 7.13-6.85 (βH, m), 4.93 (H, m), 4.41 (H, m), 3.78-3.43 (H, m), 3.13-2.60 (H, m), 2.20-1.53 (4H, m), 1.72 (3H, d), 1.27 (3H, d); $[\alpha]_D^{25}$ −71.2 (*c* 1.16, chloroform).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.2; H, 9.2; N, 7.4.

Compounds **5** and **6** were identified by comparison of their glc-retention times (glc-analysis conditions were the same reported above) and ms-fragmentation patterns with those of a 25:75 mixture obtained as described below; ms: m/e (%), 132 (100), 147 (M^+, 59), 117 (32), 18 (26), 146 (25), 130 (23), 28 (22), 118 (20), 105 (20), 39 (18).

Hydrogentation and Analysis of 7-Methylquinoline.

A sample of commercial 7-methylquinoline, 3.58 g (25 mmoles) containing about 25% of 5-methylquinoline was dissolved in 20 ml of trifluoroacetic acid, 0.38 g of platinum oxide was added and the mixture was hydrogenated at 50 psi in a Parr apparatus. After 70 minutes, when the pressure had dropped 24 psi, the catalyst was filtered off, the solution was diluted with water made carefully basic with sodium hydroxide and extracted with ether. The crude product (3.17 g) was stirred with 1 ml of acetic anhydride at 100° for 5 hours. After cooling, the mixture was diluted with 50 ml of water, 8 ml of 37% hydrochloric acid was added and the solution was extracted five times with ether. The aqueous solution was made strongly alkaline with sodium hydroxide and extracted with ether. The organic solution was dried over potassium hydroxide and the solvent evaporated. The residue was fractionally distilled to give 1.2 g of a 3:1 mixture of **6** and **5**, bp 90-95° (10 mm Hg), which was submitted to glc-ms analysis (2 m × 2 mm column packed with 15% Carbowax 20M on Chromosorb W and heated at 190°); ms: m/e (%), 147 (M^+, 100), 132 (84), 105 (65), 146 (29), 117 (25), 118 (20), 39 (20), 130 (19), 104 (16), 77 (14); nmr: (δ ppm) 7.47 (γH, d, relative to compound **5**), 7.35 (γH, d, relative to compound **6**), 1.27 (3H, d, relative to compound **5**), 1.10 (3H, d, relative to compound **6**).

(+)-*(R)*-2,5-Dimethyl-8-isopropylidene-5,6-dihydro-7*H*-quinoline (**11**).

(+)-*(R)*-Pulegon morpholino-enamine, 9.27 g (42 mmoles), purified MVK, 3.53 g (50 mmoles), in 50 ml of anhydrous benzene were refluxed for 24 hours. After evaporation of the solvent the dark residue was kept in 160 ml of acetic acid, 9.24 g (0.13 mole) of hydroxylammonium hydrochloride were added and the mixture was heated at 115° for 48 hours under nitrogen. After cooling, most of the solvent was removed *in vacuo*, 50 ml of water were added and the mixture was made alkaline with a 10% solution of sodium hydroxide. Extraction with ether, drying over sodium sulfate and bulb-to-bulb distillation gave 2.7 g of an oil, bp 60-77° (0.2 mm Hg). The glc-ms analysis (1 m × 2 mm column packed with 5% SE-30 on Chromosorb W and heated at 125°) showed the following composition of the distillate: 49% of 2,5-dimethyl-8-isopropylidene-5,6-dihydro-7*H*-quinoline (**11**), 32% of 2,5-dimethyl-8-(2-propenyl)-5,6,7,8-tetrahydroquinoline (**12**), 11% of 2,7-dimethyl-5,6,7,8-tetrahydroquinoline (**10**) and 8% of 2,5-dimethyl-5,6,7,8-tetrahydroquinoline (**9**) [11]. By preparative glc (2 m × 7 mm column packed with 5% SE-30 on Chromosorb A 70-80 mesh and heated at 150°) pure **11** and **12** were obtained.

Compound **11**.

This compound had ms: m/e (%), 113 (100), 172 (61), 200 (45), 201 (M^+, 40), 176 (32), 158 (32), 154 (32), 173 (22), 146 (17), 160 (16); nmr: (δ ppm), 7.30 (γH, d), 6.83 (βH, d), 2.50 (3H, s), 2.17 (3H, s), 1.25 (3H, d); $[\alpha]_D^{25}$

+16.33 (*c* 15.01, chloroform).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.0. Found: C, 83.4; H, 9.3; N, 6.9.

Compound **12**.

This compound had ms: m/e (%), 201 (M^+, 100), 186 (85), 200 (55), 144 (41), 158 (37), 161 (31), 184 (20), 172 (19), 202 (19), 170 (16); nmr: (δ ppm), 7.40 (γH, d), 6.90 (βH, d), 5.00-4.83 (H, m), 4.30-4.17 (H, m), 3.72-3.47 (H, m), 2.43 (3H, s), 1.73 (3H, s), 1.22 (3H, dd); $[\alpha]_D^{25}$ −19.74 (*c* 7.9, chloroform).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.0. Found: C, 83.3; H, 9.6; N, 6.9.

Compounds **9** and **10** were also isolated as a mixture by preparative glc under the same conditions. Their structures were assigned by comparison of their nmr spectrum and the analogous one recorded for the 3:1 mixture of 7-methyl- and 5-methyl-5,6,7,8-tetrahydroquinoline obtained as described above; nmr: (δ ppm), 1.27 (3H, d, relative to compound **9**), 1.10 (3H, d, relative to compound **10**).

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