

The Synthesis of 1,4,4-Trimethyl-1,2,3,4-tetrahydroquinoline, a Key Intermediate for the Preparation of Aza-arotinoids

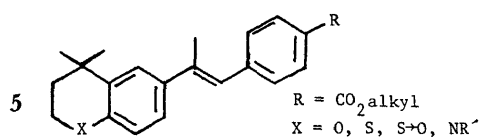
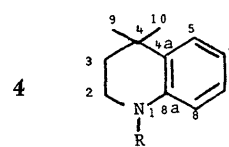
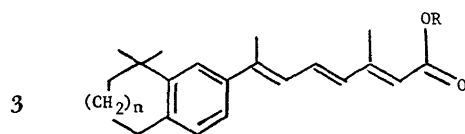
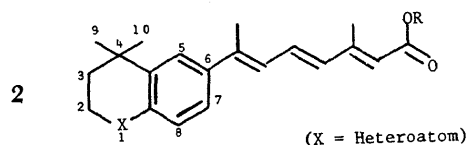
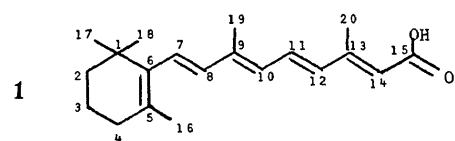
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The synthesis of 1,4,4-trimethyl-1,2,3,4-tetrahydroquinoline has been achieved starting from *N*-methylaniline. A three-step sequence was developed and gave an overall yield of 48.6%. Spectral analyses (^1H and ^{13}C NMR, IR, and mass spectral data) were in agreement with the structures of all intermediates as well as for the final product. This quinoline derivative is a key intermediate of potential use in the synthesis of nitrogen-containing retinoids, some of which in this family of heteroarotinoids have shown good activity in the tracheal organ culture assay for anticancer activity. This is the first reported synthesis of the title compound.

INTRODUCTION

Retinoids and, in particular, derivatives of retinoic acid (1), have become the center of an enormous research effort in view of the fact that specific members have shown an ability to restore cells in a premalignant state to a normal state (2). Consequently, synthetic models with structural similarities to *trans*- and *cis*-retinoic acid are current targets for the organic chemist (3). Test compounds are easily evaluated for ability to convert premalignant tracheal organ cells, derived from hamsters raised on a vitamin A deficient diet, to normal cells in cultures (1). Since it is known (4) that *trans*-retinoic acid (1) is metabolized *in vitro* via oxidation at C-4 and/or at the ring double bond (an epoxidation), compounds which might serve as mimics could include heteroatoms replacing C-4 and an aromatic ring to retard the epoxidation process. Key intermediates for the preparation of such systems as 2 are rare in the literature in spite of the activity of arotinoids 3 (the term 'arotinoids' was coined to describe retinoic acid analogs that had at least one aromatic ring present in the molecule) (5). This paper reports the preparation of 1,4,4-trimethyl-1,2,3,4-tetrahydroquinoline (4), which is potentially a useful synthon to obtain a nitrogen analog of 2.



METHODS AND MATERIALS

^1H NMR spectral data were collected with a Varian XL - 300 spectrometer. ^{13}C NMR data were obtained by using a Varian XL - 100(15) spectrometer equipped with a Nicolet TT - 100 PFT accessory. All NMR signals are reported in δ or ppm values downfield from TMS used as an internal standard. The solvent employed for all NMR analyses was DCCl_3 , unless otherwise specified. IR spectral data were taken with a Perkin-Elmer 681 spectrometer. Mass spectral data were obtained on a CEC Model 21 - 110B HR mass spectrometer.

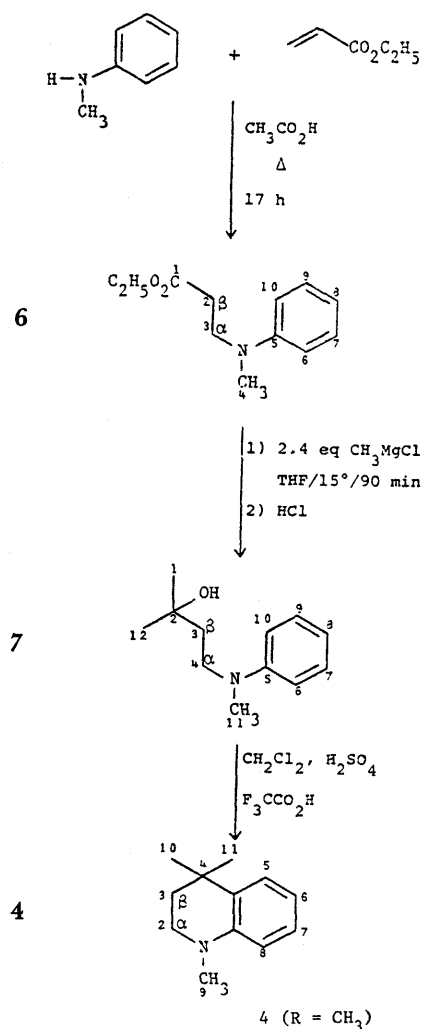
Reagents were purchased from the sources listed and were used without further purification unless otherwise specified: *N*-methylaniline (Aldrich, freshly distilled from zinc dust, bp 194 - 195 °C), ethyl acrylate (Aldrich, bp 99 °C), methylmagnesium chloride (Aldrich, 2.9 M in THF), and trifluoroacetic acid (Eastman, bp 72 °C).

Ethyl 3-phenylmethylaminopropionate (6)

A mixture of freshly distilled *N*-methylaniline (267.5 g, 2.50 mol) and glacial acetic acid (50 mL) was placed in a 1-liter, 3-necked flask equipped with a condenser and CaCl_2 tube and an additional funnel charged with ethyl acrylate (250 g, 2.50 mol). The flask was warmed on a steam bath and the ethyl acrylate was added dropwise over a 25-min period. The resulting yellow solution was heated with occasional swirling for 17 hr, during which time it turned deep red. This solution was then washed with 5% NaHCO_3 (4×75 mL) and then with brine (3×75 mL). During the first wash, an emulsion often formed that could be destroyed by the addition of 50 mL of diethyl ether. After drying (MgSO_4) the solution was evaporated to give a red oil which was distilled to yield 404.5 g (78.2%) of **6** as a yellow oil: bp 105-109 °C/0.2 mmHg (lit (6) 98-100 °C/0.05 mmHg); IR (neat) cm^{-1} 1740 (C = O); ^1H NMR (DCCl_3) δ 1.15 [t, 3 H, OCH_2CH_3], 2.46 [t, 2 H, $\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $J = 7.08$ Hz], 2.80 [s, 3 H, NCH_3], 3.59 [t, 2 H, NCH_2 , $J = 7.08$ Hz], 4.04 [q, 2 H, OCH_2CH_3], 6.67 [m, 3 H, *o*- and *p*-H of ArH], 7.18 [m, 2 H, *m*-H of ArH]; ^{13}C NMR (DCCl_3) ppm 14.1 [OCH_2CH_3], 31.6 [C-2], 37.0 [C-4], 48.4 [C-3], 60.2 [OCH_2], 112.3 [C-6, 10], 116.5 [C-8], 129.0 [C-7, 9], 148.4 [C-5], 171.7 [C-1]; molecular ion from mass spectrum (u): calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$: 207.1259; found: 207.1261.

2-Methyl-4-(phenylmethylamino)-2-butanol (7)

A solution of methylmagnesium chloride (414 mL, 1.20 mol) in a 1-liter, 3-necked, round-bottom flask along with a magnetic stirring bar. The flask was also equipped with a thermometer, a dry-ice-cooled condenser (with CaCl_2 tube), and an addition funnel charged with ethyl 3-phenylmethylaminopropionate (**6**, 100 g, 0.483 mol). The apparatus was flushed with N_2 and the flask was cooled to -5 °C in an ice-salt bath. The ester **6** was then added dropwise at such a rate as to maintain the temperature below 15 °C (45 min). After warming slowly to room temperature, the solution was



stirred for 90 min. Decomposition was accomplished by pouring the mixture onto crushed ice and 85 mL of conc HCl with stirring. Water was added slowly to dissolve precipitated salts and the solution was then neutralized by the addition of K_2CO_3 (50 g). Two layers separated and the aqueous layer was extracted ($HCCl_3$, 3×100 mL). The combined organic layer and extracts were dried (K_2CO_3), and the solvent was evaporated to give an orange oil. Distillation of this oil gave 74.7 g (80.1%) of **7** as a pale yellow liquid: bp 95 - 99 °C/0.08 mmHg; IR (neat) cm^{-1} 3150 - 3650 (O-H); 1H NMR ($DCCl_3$) δ 1.62 [s, 6 H, $HOC(CH_3)_2$], 2.06 [t, 2 H, NCH_2CH_2 , $J = 7.82$ Hz], 3.24 [s, 3 H, NCH_3], 3.34 [s, 1 H, OH], 3.81 [t, 2 H, m -H of ArH]; ^{13}C NMR ($DCCl_3$) ppm 29.3 [C-1, 12], 38.1 [C-11], 38.5 [C-3], 48.5 [C-4], 69.8 [C-2], 112.8 [C-6, 10], 116.5 [C-8], 128.9 [C-7, 9], 149.1 [C-5]; molecular ion from mass spectrum (u): calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1464.

1,4,4-Trimethyl- 1,2,3,4-tetrahydroquinoline (**4**, R = C H₃)

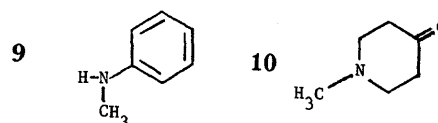
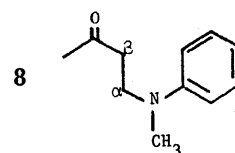
A solution of **7** (21.3 g, 0.110 mol) in H_2CCl_2 (350 mL) was placed in a 500-mL, round-bottom flask equipped with a magnetic stirrer. To this was added cautiously a solution of F_3CCO_2H (5 mL) in conc H_2SO_4 (50 mL). The resulting mixture was boiled for 3 h after which time the H_2CCl_2 was evaporated. The residue was neutralized by the addition of a saturated aqueous solution of K_2CO_3 . The resulting slurry was extracted with $HCCl_3$ (3×75 mL), and the combined extracts were washed with 5% $NaHCO_3$ (3×50 mL) and then with brine (2×50 mL). After drying (K_2CO_3), the solution was evaporated to give a red oil which was distilled to yield **4** (14.8 g, 77.1%) as a colorless oil: bp 137 - 139 °C/0.06 mmHg; 1H NMR ($DCCl_3$) δ 1.24 [s, 6 H, $C(CH_3)_2$], 1.69 [t, 2 H, NCH_2CH_2 , $J = 5.96$ Hz], 2.79 [s, 3 H, NCH_3], 3.11 [t, 2H, NCH_2 , $J = 5.94$ Hz], 6.51- 7.14 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$) ppm 31.0 [C-10, 11], 31.9 [C-4], 37.3 [C-3], 39.2 [C-9], 47.6 [C-2], 131.2 [C-4a], 145.3 [C-8a]; signals were also visible at 110.8, 116.1, 125.7 and 126.7 ppm but these could not be assigned unequivocally to C-5—C-8. Molecular ion from mass spectrum: calcd for $C_{12}H_{17}N$: 175.1361; found: 175.1358.

N-Methylaniline (**9**)

The ^{13}C NMR spectrum recorded in dioxane gave signals at 30.2 (H_3C), 112.3 [C-2], 116.7 [C-4], 129.2 [C-3], and 150.2 [C-1] ppm (**7**).

N-Methyl-4-piperidone (**10**)

The ^{13}C NMR spectrum recorded neat gave signals at 40.89 [C-3], 45.14 [CH_3], 55.4 [C-2], and 206.2 [C-4] ppm (**8**).



RESULTS AND DISCUSSION

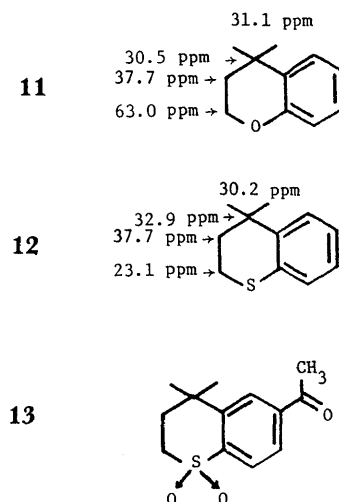
Our continuing interest in the chemistry of retinoids, and in particular heteroarotinoids (**9**), has prompted us to report here the synthesis of the title compound. The latter is a key intermediate in the synthesis of nitrogen-containing retinoids. In fact, a recent patent (**10**) indicates that a few examples of **5** have been prepared including the nitrogen analog illustrated.

Our synthesis of **4** (R = CH_3) is outlined in the Scheme shown. The acid-catalyzed Michael type of addition of *N*-methylaniline (**9**) to ethyl acrylate proceeded in a yield of 78.2% with respect to amino ester **6**. The addition of a slight excess of methylmagnesium chloride in THF afforded the tertiary alcohol **7** (80.1%). Although a number of cyclization techniques were employed for the conversion of **7** to the title compound **4** (R = CH_3), the best involved treatment of the alcohol with a combination of F_3CCO_2H/H_2SO_4 in H_2CCl_2 . A simple workup provided, after distillation, **4** as a colorless oil.

Spectral analysis of ester **6** was performed via 1H and ^{13}C NMR techniques. An expected triplet for the proton signal for the CH_2 group

alpha to the nitrogen occurred at δ 3.59 with another triplet for the CH₂ protons beta to the nitrogen at δ 2.46. The alcohol **7** had similar signals at δ 3.81 and 2.06, respectively. Proton signals for the methyl groups attached to nitrogen were visible at 2.80 (**6**) and 3.24 (**7**). Model system **8** (**11**) had proton signals for the CH₂ groups at δ 3.66 (H- α) and 2.70 (H- β), respectively. In the title compound (**4**, R = CH₃), signals for the protons (α and β) in comparable positions occurred at δ 3.11 and 1.69, respectively. A singlet for the protons on the geminal methyl groups was visible at δ 1.24 while the protons on the methyl attached to nitrogen appeared at δ 2.79. Other data are in the METHODS AND MATERIALS section.

¹³C NMR analysis proved especially useful with the observation of splitting patterns from off-resonance techniques and by comparison with the spectra of model compounds **9** and **10**. The ¹³C resonance for C- α in ester **6** occurred at 48.4 ppm while C- β was at 31.6 ppm and the CH₃ attached to nitrogen at 37.9 ppm. The comparable carbons in the alcohol **7** had signals at 48.5, 38.5, and 38.1 ppm, respectively. In the final product **4** (R = CH₃), these resonances were at 47.6, 37.3, and 39.2 ppm, respectively, while the carbons of the geminal methyl groups appeared at 31.0 ppm. The tertiary carbon of the partially saturated ring [C-4] had a signal at 31.9 ppm. It is worthy of note that in the corresponding oxygen and sulfur counterparts, namely **11** and **12**, the ¹³C NMR signals shown (9) closely parallel those of **4** (R = CH₃) except, of course, that for the C- α , the position of which is highly dependent upon the electronegativity of the atom (12). Since the structure of **12** was confirmed via an X-ray (9) diffraction analysis of the sulfone derivative **13**, the identification of **4** (R = CH₃) seems secure.



ACKNOWLEDGMENT

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