Synthesis of Substituted 5,6,7,8-Tetrahydroquinolines from Conjugated Ketoximes

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A number of 5,6,7,8-tetrahydroquinolines have been prepared by heating conjugated ketoximes at 300° in a sealed tube.

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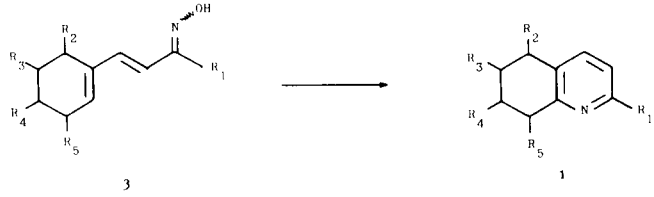
It has been reported that conjugated ketoximes can be transformed into pyridines by heating at extremely high temperatures [1]. However, neither accurate experimental procedures nor yields in aromatic products have been described.

In this paper we report the preparation of 2-methyl-5,6,7,8-tetrahydroquinolines bearing alkyl groups **1e,f** or bridged at the alicyclic moiety **1g** and 2-alkyl- or 2-aryl-5,6,7,8-tetrahydroquinolines **1a-d** by thermal electrocyclic reaction of conjugated ketoximes **3**, according to Scheme 1.

Scheme 1



1a-3a, R_1 CH_3, R_2 R_3 R_4 R_5 H

1b-3b, R_1 n-C_4H_9, R_2 R_3 R_4 R_5 H

1c-3c, R_1 t-C_4H_9, R_2 R_3 R_4 R_5 H

1d-3d, R_1 C_6H_5, R_2=R_3 R_4 R_5=H

1e-3e, R_1 R_4=CH_3, R_2=R_3=R_5=H

1f-3f, R_1 R_3 R_5=CH_3, R_2=R_4 H

1g-3g, R_1 CH_3, R_2 R_4 [...],  , R_3=R_5 H

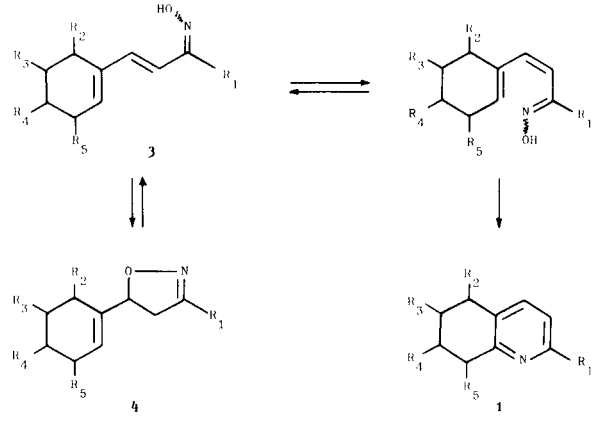
Conjugated ketones **2** were obtained in high yields through an aldol condensation of the proper aldehyde with a methyl ketone [2]. Treatment of dienones **2** with hydroxylammonium hydrochloride gave the desired oximes **3** (Scheme 2).

In Table I, physical, analytical and spectral data of prepared ketones are reported together with melting points of some oximes [3].

Cyclization of ketoximes **3** was first carried out at 300° C and at atmospheric pressure. In these conditions, tetrahydroquinoline **1** and dihydroisoxazole **4** [7] (Scheme 3) were obtained in about 1:1 ratio, the yield of **1** ranging from 25 to 31%. When the reaction was accomplished in a sealed tube, at the same temperature, the yield in tetrahydroquinoline was enhanced up to 43% (Table II, **1e**), while formation of **4** was not observed at all. Moreover, heating of **4a** in a sealed tube at 300° afforded **1a** as the only product in about 50% yield.

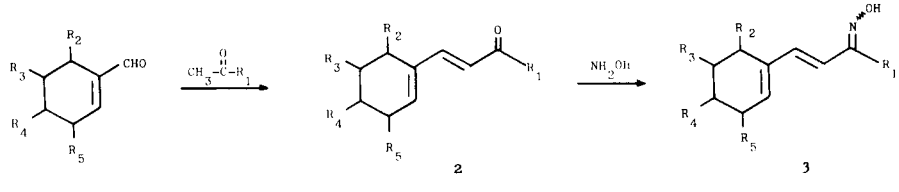
These facts suggest that the following equilibria are involved in the formation of the products (Scheme 3).

Scheme 3



Only in the case of **1c** the yield resulted very poor (<5%) (Table II), the formation of **4c** prevailing by far. This fact is probably due to the severe interaction between

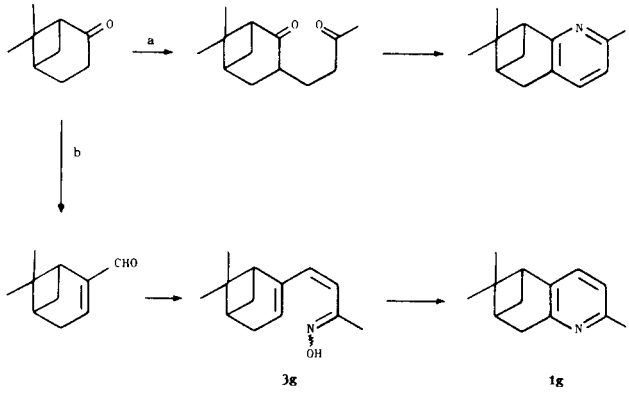
Scheme 2



the bulky *t*-butyl and the hydroxyl group in *cis*-oxime (Scheme 3).

It is noteworthy that, starting from alkyl or bridged cyclohexanones, this synthetic method leads to alkylsubstituted 5,6,7,8-tetrahydroquinolines which are isomerically related to those obtainable, from the same substrates, *via* 1,5-dioxocompounds [11]. The synthesis of the two isomeric 2,7,7-trimethyl-5,6,7,8-tetrahydro-6,8- [12] (Scheme 4, pathway A) and 2,6,6-trimethyl-5,6,7,8-tetrahydro-5,7-methanoquinoline (**1g**) (Scheme 4, pathway B) provides a significant example of this possibility.

Scheme 4



3g 1g

EXPERIMENTAL

Boiling points are uncorrected. The gc analyses were performed on a Perkin-Elmer 3920-B gas chromatograph, using 2 m x 2 mm column packed with 10% SP-1000 on Supelcoport 80-100 mesh and heated at 170°C. The nmr spectra were obtained with a Varian T-60 spectrometer in tetrachloromethane or deuteriochloroform solutions using tetramethylsilane as an internal standard (δ = 0). The optical rotations were taken on a Perkin-Elmer 241 polarimeter in 1 dm tubes. Elemental analyses were performed on a Perkin-Elmer 240-B analyzer.

Materials.

1-Cyclohexen-1-carboxaldehyde was prepared according to Heilbron, *et al.* [4]. 4-Methyl-1-cyclohexen-1-carboxaldehyde was obtained according to Nazarov, *et al.* [13]. (-)-Myrtenal was obtained according to Semmler, *et al.* [14].

3,5-Dimethyl-1-cyclohexen-1-carboxaldehyde.

This compound was prepared in 60% yield by α-bromination of 3,5-dimethyl-1-carboxaldehyde [15] followed by dehydrohalogenation of the halogen derivative, according to Heilbron, *et al.* [4], bp 75° at 10 mm Hg; nmr (deuteriochloroform): δ 9.27 (1 H, s), 6.57-6.35 (1 H, m).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.04; H, 10.40.

Conjugated Ketones **2a,e,f,g**. General Procedure.

A solution of the α,β-unsaturated aldehyde (0.1 mole) in acetone (25 ml) was slowly added to a solution of sodium hydroxide (0.03 mole) in a 1:2.5 water-acetone mixture (140 ml). After the addition was completed, the solution was stirred for 3 hours. The unreacted acetone was distilled off and the residue was extracted with ether (2 x 25 ml). Drying over sodium sulfate, evaporation of the solvent and distillation *in vacuo* afforded pure conjugated ketones. Yields, physical, analytical and spectral data are collected in Table I.

Table I

Physical, Analytical and Spectral Data of Conjugated Ketones

Compound	Yield [a] %	Reaction Time/hrs	BP °C mm Hg	Molecular formula	Analysis % Calcd./Found C	H	NMR (Carbon tetrachloride) (ppm)
2a [b]	93	3	102/3 [c]				6.88 (βH, d, J = 16 Hz), 6.15-5.88 (δ H, m), 5.82 (αH, d, J = 16 Hz), 2.10 (3 H, s)
2b	70	24	135/0.8	$C_{13}H_{20}O$	81.20 81.04	10.48 10.56	7.06 (βH, d, J = 16 Hz), 6.23-6.10 (δ H, m), 6.00 (αH, d)
2c [d]	40	24	140/0.3	$C_{13}H_{20}O$	81.20 81.23	10.48 10.36	7.08 (βH, d, J = 15 Hz), 6.25 (αH, d, J = 15 Hz), 6.12-6.00 (δ H, m), 1.12 (9 H, s)
2d	30	10 [e]	67-8 [f]				8.00-7.75 (2 H, m), 7.75-7.15 (4 H, m), 6.77 (αH, d, J = 15 Hz), 6.35-6.13 (δ H, m)
2e	90	3	126/3 [g]				7.05 (βH, d, J = 16 Hz), 6.10-5.93 (αH, d, J = 16 Hz), 5.90 (δ H, m), 2.22 (3 H, s), 1.04 (3 H, d)
2f [h]	73	3	87/1	$C_{12}H_{18}O$	80.85 80.97	10.18 10.29	7.06 (β H, d, J = 16 Hz), 6.03-5.86 (δ H, m), 6.00 (α H, d, J = 16 Hz), 2.23 (3 H, s), 1.17-0.77 (6 H, m)
2g [i]	70	3	90/0.05	$C_{13}H_{18}O$	82.06 82.16	9.53 9.48	7.05 (β H, d, J = 16 Hz), 6.00 (δ H, m), 5.93 (α H, d, J = 16 Hz), 2.23 (3 H, s), 1.33 (3 H, s), 0.76 (3 H, s)

[a] Isolated yields. [b] Oxime, mp 70-73°. [c] 64/0.1 [4]. [d] Oxime, mp 119-120°. [e] The reaction was carried out at 0°. [f] Melted 68.5-69.5 [5]. [g] 70-72 [6]. [h] Oxime, mp 67-68°. [i] Oxime, mp 145°.

Table II

Physical, Analytical and Spectral Data of 5,6,7,8-Tetrahydroquinolines

Compound	Yield [a] %	BP °C mm Hg	Molecular formula	Analysis % Calcd./Found C	H	N	NMR (Carbon tetrachloride) (ppm)
1a	40	92/10 [b]					7.03 (γ H, d, J = 7 Hz), 6.67 (β H, d, J = 7 Hz), 3.03-2.50 (3 H, s), 2.00-1.60 (4 H, s)
1b	42	81/0.1	$C_{13}H_{19}N$	82.48 82.34	10.12 9.96	7.40 7.25	7.20 (γ H, d, J = 7 Hz), 6.80 (β H, d, J = 7 Hz), 3.10-2.50 (4 H, m), 2.10-1.21 (10 H, m), 1.00 (3 H, d)
1c	<5 [c]		$C_{13}H_{19}N$	82.48 82.72	10.12 10.20	7.40 7.31	7.17 (γ H, d, J = 7 Hz), 6.93 (β H, d, J = 7 Hz)
1d	41 [d]	118/0.1 [e]					8.04-7.71 (2 H, m), 7.55-7.08 (5 H, m), 3.13-2.53 (4 H, m), 2.17-1.56 (4 H, m)
1e	43	140/10 [f]					7.22 (γ H, d, J = 7 Hz), 6.85 (β H, d, J = 7 Hz) 3.10-2.60 (4 H, m), 2.33-1.50 (3 H, m), 1.08 (3 H, d)
1f	20	68/0.2	$C_{12}H_{17}N$	82.23 81.98	9.78 10.01	7.99 7.70	7.00 (γ H, d, J = 8 Hz), 4.66 (β H, d, J = 8 Hz), 2.40 (3 H, s)
1g [g]	25	72/0.1	$C_{13}H_{17}N$	83.37 83.25	9.15 9.00	7.48 7.37	6.88 (γ H, d, J = 7 Hz), 6.58 (β H, d, J = 7 Hz), 2.93 (2 H, d), 2.75-2.46 (2 H, m), 2.40 (3 H, s), 2.17-1.55 (2 H, m), 1.37 (3 H, s), 0.63 (3 H, s)

[a] Yield of the isolated product. [b] 101-104/13 [8]. [c] Isolated by preparative gc. [d] The starting oxime was heated under atmospheric pressure. [e] 214-216/15 [9]. [f] 60/0.2 [10]. [g] $[\alpha]_D^{25}$ -35.94 (c 1.74, cyclohexane).

Conjugated Ketones **2b,c,d**. General Procedure.

To a solution of cyclohexene-1-carboxaldehyde (0.01 mole) and the proper ketone (0.01 mole) in ethanol (15 ml), a 10% aqueous solution of sodium hydroxide (8 ml) was added. The solution was stirred at room temperature, diluted with water (50 ml) and extracted with ether (2 x 20 ml). The combined ether extracts were dried over sodium sulfate and the solvent was evaporated. The crude conjugated ketone was purified by distillation under reduced pressure. Reaction times, yields, physical, analytical and spectral data are reported in Table I.

Tetrahydroquinolines. General Procedure.

The oxime (0.01 mole) was heated at 300° in a sealed tube for 15 minutes. After cooling, the mixture was treated with a 10% solution of hydrochloric acid and extracted with ether. The aqueous phase was alkalized with a 10% solution of sodium hydroxide and extracted with ether. The organic extract was dried over sodium sulfate, the solvent was evaporated and the quite pure tetrahydroquinoline (>95% by gc) was recovered by distillation under reduced pressure. Yields, physical, analytical and spectral data are reported in Table II.

Isolation of **4a,b,c**.

Ketoximes **3a,b,c** (0.01 mole) were heated at 300° for 15 minutes under atmospheric pressure. After cooling, the mixture was acidified with a 10% solution of hydrochloric acid and extracted with ether. The organic phase was separated, dried over sodium sulfate and the solvent removed *in vacuo*. The oily residue was distilled under reduced pressure to afford the title compounds in the pure state.

Compound **4a**.

This compound was obtained in 26% yield, bp 120° (2 mm Hg); nmr (deuteriochloroform): δ 5.85-5.57 (1 H, m, CH=), 4.83 (1 H, t, CH-O, J = 9 Hz), 2.98-2.82 (1 H, m), 2.82-2.63 (1 H, m), 1.95 (3 H, d, J = 1 Hz).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.44; H, 9.38; N, 8.27.

Compound **4b**.

This compound was obtained in 28% yield, bp 155° (1.5 mm Hg); nmr (deuteriochloroform): δ 5.85-5.60 (1 H, m, CH=), 4.83 (1 H, t, CH-O, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.58; H, 10.08; N, 6.51.

Compound **4c**.

This compound was obtained in 56% yield, bp 150° (1.5 mm Hg); nmr (deuteriochloroform): δ 5.77-5.57 (1 H, m, CH=), 4.83 (1 H, t, CH-O, J = 9 Hz), 2.88 (1 H, d, J = 9 Hz), 2.82 (1 H, d, J = 9 Hz), 1.17 (9 H, s).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.09; H, 10.32; N, 6.54.

Conversion of **4a** into **1a**.

Compound **4a** (0.41 g, 2.5 mmoles) was heated at 300° in a sealed tube for 15 minutes. The isolation of the tetrahydroquinoline was achieved following the same experimental procedure previously described. The yield of **1a** was 0.17 g (47%). Physical and spectral data were coincident with those reported in Table II.

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[3] Oximes **3a,c,f,g** were obtained as solids and were recrystallized from *n*-hexane; derivatives **3b,d,e** were obtained as oils and were submitted to thermal cyclization without any purification.

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