

Alexander L. Weis,\* Felix Frolow and Rosita Vishkautsan

Department of Organic Chemistry, The Weizmann Institute of Science,  
Rehovot 76100, Israel  
Received April 24, 1985

Optically active condensed derivatives of hydroxytetrahydropyrimidines and dihydropyrimidines were prepared by condensation of (+)pulegone with amidines and guanidine. The structure, the possible mechanism of formation of these compounds, and the existence of amidinic tautomerism are discussed on the basis of the measured spectral data and x-ray diffraction analysis.

*J. Heterocyclic Chem.*, **23**, 705 (1986).

Over the past decade, chiral heterocycles have proven extremely useful as auxiliary reagents in asymmetric syntheses [2]. Successful development of a versatile and highly efficient condensation for the preparation of previously unknown hydroxytetrahydro- and dihydropyrimidines [3] stimulated our desire to design optically active compounds containing these moieties. Such enantiomerically pure pyrimidine derivatives would constitute novel "asymmetric induction adjuvants" [4], enabling synthesis of chiral acids, aldehydes, tertiary alcohols, and amines. In addition, related compounds containing the guanidinium moiety would represent a new series of pharmaceutically interesting sodium-channel blockers [5]. Moreover, these chiral derivatives can serve as chromatographic stationary phases [6] for enantiomeric separation of a series of previously prepared racemic tetrahydro- and dihydropyrimidines. Since the above-mentioned condensation method involves reaction of  $\alpha,\beta$ -ethylenic carbonyl derivatives and amidines, we searched for an optically active, easily available, inexpensive compound containing an  $\alpha,\beta$ -unsaturated carbonyl fragment for use in this condensation. One such convenient molecule is naturally occurring enantiomerically pure *R*(+)pulegone (from oil of pennyroyal), which is widely used in the perfume industry.

Herein, we report the preparation of optically active compounds containing the dihydro- or tetrahydropyrimidinic ring by the condensation of *R*(+)pulegone with amidines and guanidines.

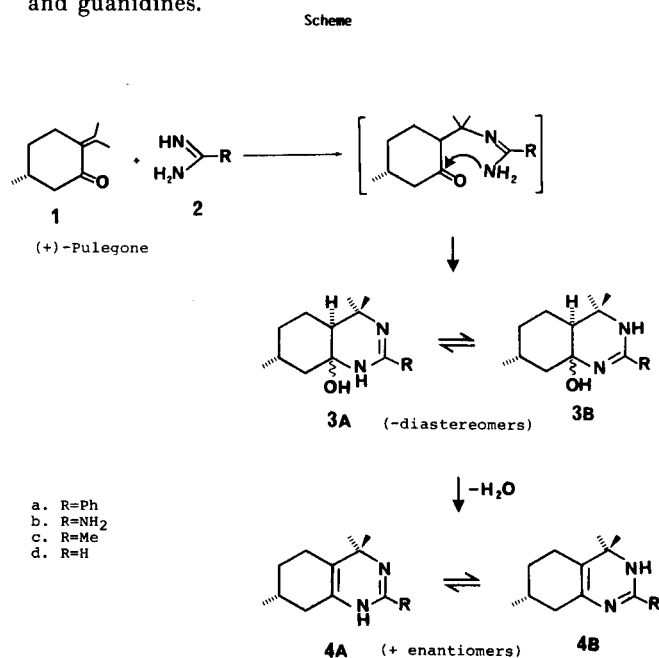


Table 1

Analytical data for Quinazoline Products 3 and 4

Compound	R	Yield, %	mp, °C	[a] <sub>D</sub> <sup>20</sup> (1.0, CH <sub>3</sub> OH)	Formula	M.W. (ms)	Elemental Analysis					
							Calcd [a]			Found		
							C	H	N	C	H	N
<b>3c</b>	CH <sub>3</sub>	63	175-176 (from acetone)	-22.2°	C <sub>12</sub> H <sub>22</sub> N <sub>2</sub> O	210.3 (210)	68.53	10.54	13.32	68.34	10.54	13.58
<b>3d</b>	H	38	162 (from acetone)	-34.2°	C <sub>11</sub> H <sub>20</sub> N <sub>2</sub> O	196.3 (196)	67.31	10.27	14.27	67.20	10.40	14.46
<b>4a</b>	Ph	72.5	142-144 (from benzene)	+37.1°	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub>	254.4 (254)	80.27	8.72	11.01	80.00	9.08	10.90
<b>4b</b>	NH <sub>2</sub>	70	183-185	+64.4°	C <sub>11</sub> H <sub>19</sub> N <sub>3</sub>	193.3 (193)	68.35	9.91	21.74	68.01	9.83	22.02
<b>4c</b>	CH <sub>3</sub>	68	155-156 (sublimation)	+20.7°	C <sub>12</sub> H <sub>20</sub> N <sub>2</sub>	192.3 (192)	74.95	10.48	14.57	74.74	10.55	14.73

[a] Taken from G. H. Stout, "Composition Tables", W. A. Benjamin, New York, 1963.

Table 2  
Selective Spectral Data of Quinazolines **3** and **4**

Cpd	R	$2\text{CH}_3$ at 4	$\text{CH}_3$ at 7	$^1\text{H}$ NMR $\text{CH}_2$ (m) [a]	NH (OH) [b]	$^{13}\text{C}$ NMR	IR ( $\nu$ , $\text{cm}^{-1}$ ) potassium bromide	chloroform	UV $\lambda$ max ( $\epsilon$ ) (ethanol)
<b>3c</b>	1.89 (s, 3H)	1.25 (s, 3H)	0.90	0.83-1.85	3.38 (bs)	153.03, 76.96,	3342, 3276, 2947,	3590, 3432, 1656,	208 (8255)
		1.17 (s, 3H)	(d, 3H, J = 6.0 Hz)			51.73, 49.85, 49.72, 47.81, 35.29, 31.65, 28.91, 24.00, 22.22, 22.03	2919, 2864, 2840, 1619, 1550, 1532, 1466, 1456, 1444, 1426, 1384, 1365, 965	1650, 1626, 1509, 1505, 1458, 1439, 1432, 1388, 1368	
<b>3d</b>	6.99 (s, 1H)	1.18 (s, 3H)	0.91	0.90-1.88	2.70 (bs)	143.52, 80.81,	3206, 2950, 2924,	3934, 1672, 1647,	208 (4308)
		1.27 (s, 3H)	(d, 3H, J = 6.0 Hz)			52.62, 50.43, 36.51, 31.69, 29.85, 23.94, 23.85, 22.46	2866, 2947, 1650, 1631, 1613, 1571, 1466, 1455, 1448, 1378, 1370, 1320, 1260, 1178, 991	1611, 1583, 1457, 1385, 1373, 1370, 1311	
<b>4a</b>	7.76-7.36 (m, 5H)	1.30 (s, 3H)	1.01	1.02-2.11	3.97 (bs)	153.19, 151.58,	3224, 3055, 2973,	3423, 1643, 1593,	319 (3262)
		1.32 (s, 3H)	(d, 3H, J = 5.9 Hz)			146.09, 136.04, 129.97, 128.45, 126.41, 104.71, 53.36, 37.98, 31.31, 29.04, 28.74, 23.14, 21.58	2963, 2946, 2925, 2911, 2864, 2844, 2831, 1649, 1592, 1582, 1557, 1520, 1492, 1453, 1380, 1371, 1357	1563, 1508, 1504, 1470, 1455, 204 (14174) 1361	
<b>4b</b>	-	1.20 (s, 6H)	0.96	0.94-2.04	3.13 (bs)	168.71, 128.01,	3224, 3162, 3153,	3337, 3236, 1685,	254 (3384)
		(d, 3H, J = 5.1 Hz)	126.49, 111.54, 53.41, 34.39, 30.91, 28.26, 28.10, 22.20, 21.39			3042, 2934, 2920, 2912, 2872, 2848, 3831, 1692, 1656, 1619, 1590, 1537, 1455, 1438, 1386, 1374, 1357	1675, 1653, 1646, 1636, 1623, 1616, 1576, 1559, 1457		
<b>4c</b>	1.96 (s, 3H)	1.23 (s, 6H)	0.98	0.98-2.08	3.13 (bs)	152.04, 151.86,	3168, 2961,	3423, 1700, 1652,	260 (5645)
		(d, 3H, J = 5.6 Hz)	132.16, 120.25, 53.36, 37.27, 31.32, 29.01, 28.96, 22.85, 22.64, 21.53			2865, 2853, 2834, 1650, 1598, 1580, 1455, 1437, 1384, 1364, 1354, 1234, 1177	1650, 1607, 1498, 1479, 1459, 1431, 1384, 1369, 1361		

[a] In all  $^1\text{H}$  nmr spectra, protons of  $\text{CH}_2$  from the cyclohexane ring of (+)pulegone appeared as a multiplet and were hidden under methyl signals. [b] The position of NH/OH protons changes with the quality (purity) of the solvent used. [c] The  $^{13}\text{C}$  nmr spectrum was measured in deuteriomethanol, and some signals are hidden under solvent signals.

## Results and Discussion.

Tables 1 and 2 fully describe several novel products obtained by reacting (+)pulegone (**1**) and benzamidine (**2a**), guanidine (**2b**), acetamidine (**2c**), or formamidine (**2d**).

According to the reaction mechanism proposed earlier [7] (see Scheme), this condensation proceeds *via* 1,4-addition of the amidine **2** across the  $\alpha,\beta$ -unsaturated carbonyl fragment (Michael addition), followed by ring closure to the cyclic carbinolamine **3**, which can be further dehydrated to hexahydroquinazoline **4**.

Condensation of **1** with **2a**, **2b**, or **2c** in boiling benzene with azeotropic removal of the water released gave directly, according to elemental analysis and spectral data, the dihydropyrimidine-containing compounds **4a**, **4b**, and **4c**. However, the condensation of **2d** under the same conditions gave only the intermediate hydroxytetrahydropyrimidine-ring-containing compound **3d**, usually in low yield. In an attempt to isolate the 9-hydroxyoctahydroquinazoline (carbinolamine) intermediates **3a**, **3b**, and **3c** postulated to form during the condensation, we applied a two-step procedure involving mild conditions (acetone, 0-5°), previously used successfully for making hydroxytetrahydropyrimidines [3]. Surprisingly, we were unable to prepare **3a** and **3b** by this approach, although **3c** and **3d** did precipitate from the reaction mixture. In fact, even under these mild conditions the reactions went all the way, yielding **4a** and **4b** (as monitored by tlc), although at reduced rates compared to their formation in boiling benzene. This result exemplifies the extreme ease of dehydration of **3a** and **3b**. However, when we attempted to dehydrate **3c** and **3d** using molecular sieves or azeotropic removal of water (the second part of the two-step synthesis we developed), **4c** was isolated in only very low yield and **4d** was undetected. These latter compounds were finally prepared by dehydration with acid catalysis (acetic anhydride or phosphoryl chloride).

Since compounds **3a** and **3b** dehydrate spontaneously and could not be isolated, we had to confine our structural studies on this family of compounds to **3c** and **3d**. Usually these products are formed as a mixture of diastereomers whose optical activity depends upon workup and solvents used. We were, however, able to prepare single crystals of optically pure **3d** (see experimental), which we used for an

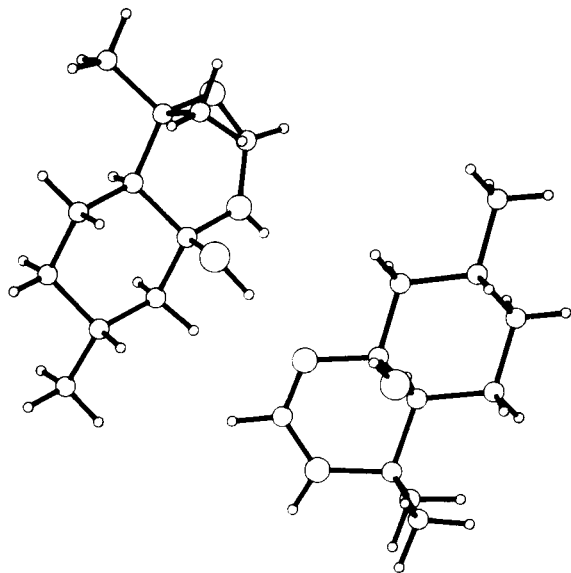


Figure 1. The pair of two independent molecules A and B connected via hydrogen bond OA(11)...NB(1) (2.73 Å).

x-ray diffraction study. The analysis shows that the crystals obtained are composed of two independent tautomeric molecules, A and B (see Figure 1), connected by three hydrogen bonds (see Table 8). The  $^{13}\text{C}$  nmr analyses of solutions of these single crystals in deuteriomethanol confirm the existence of two tautomers. This observation implies that interconversion between the forms is slow. In other solvents, the concentration ratio of the two forms depends upon solvent polarities.

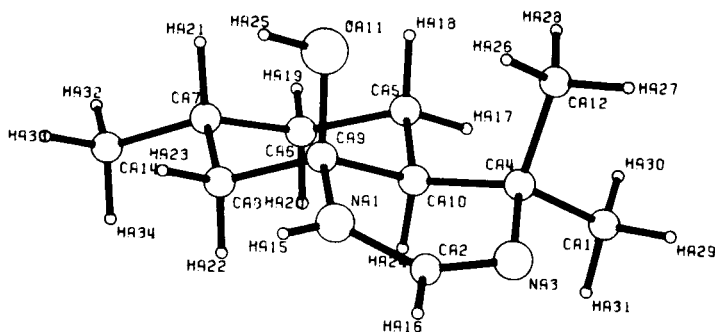


Figure 2. Computer-drawn molecular structure of (-)-7R, 9S, 10S-4,4,7-trimethyl-9-hydroxy-1,4,5,6,7,8,9,10-octahydroquinazoline (**3d**-tautomer A).

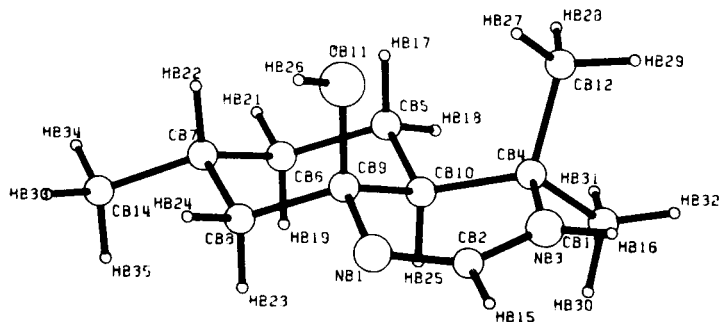


Figure 3. Computer-drawn molecular structure of (-)-7R, 9S, 10S-4,4,7-trimethyl-9-hydroxy-3,4,5,6,7,8,9,10-octahydroquinazoline (**3d**-tautomer B).

From the x-ray data, molecule A (Figure 2) has an amidinic proton at N(1) and a double bond (1.2877 Å) between C(2) and N(3). In its double-ring structure (fused at C(9) and C(10)), part of it is in a chair conformation, while the hydroxytetrahydropyrimidine ring forms a half-chair structure. The H at C(10) and the hydroxy group at C(9) are axial with a *trans* disposition. Molecule B has the same shape as A, except that the proton is on N(3) and the double bond (1.286 Å) is between C(2) and N(1) (Figure 3). This is the first observation of two resolved amidinic tautomeric forms of hydroxytetrahydropyrimidines. It is interesting to note that solid-state Fourier-transform infrared spectrum of these single crystals shows two sets of absorption bands for tautomers; for example, the C=N absorptions appear at 1641 and 1621  $\text{cm}^{-1}$ . Detailed investigation

of the rate of proton transfer in solution, as well as the structures of the **3c** pair and the second diastereomer of **3d**, which could have a *cis*-fused ring, is in progress.

According to ir spectral data, **4a** and **4c** exist as single 3,4-dihydro tautomers in the solid state (see Table 2). Compound **4a** is yellow, whereas all other synthesized compounds are white crystalline materials. In solution, all prepared dihydro compounds **4** are found in tautomeric 1, 4/3, 4 equilibria, as reported earlier for analogous systems [7,8]. However, it is difficult to distinguish two tautomers with <sup>1</sup>H nmr, as their chemical shifts are mainly identical. <sup>13</sup>C nmr is much more informative and provides a clear confirmation of the existence of the two isomers of **4**.

Table 3  
Atom Coordinates (x10<sup>4</sup>)

	x/a	y/b	z/c
NA(1)	4814(2)	2591(2)	4698(1)
CA(2)	4641(2)	1268(3)	4790(1)
NA(3)	5204(2)	291(2)	4512(1)
CA(4)	6235(2)	652(2)	4066(1)
CA(5)	6787(3)	2528(3)	3281(1)
CA(6)	6131(3)	3742(3)	2977(1)
CA(7)	5769(3)	4874(2)	3411(1)
CA(8)	4956(2)	4306(2)	3925(1)
CA(9)	5648(2)	3134(2)	4227(1)
CA(10)	5880(2)	2003(2)	3774(1)
OA(11)	6881(2)	3553(2)	4462(1)
CA(12)	7562(3)	648(3)	4395(1)
CA(13)	6237(3)	-467(3)	3596(1)
CA(14)	5046(3)	5992(3)	3086(1)
NB(1)	6540(2)	5696(2)	5209(1)
CB(2)	6080(3)	6794(2)	4989(1)
NB(3)	5664(2)	7896(2)	5272(1)
CB(4)	5580(2)	8002(2)	5926(1)
CB(5)	5907(3)	6501(3)	6853(1)
CB(6)	5835(3)	5055(3)	7075(1)
CB(7)	6828(3)	4146(3)	6758(1)
CB(8)	6651(3)	4259(2)	6081(1)
CB(9)	6733(2)	5702(2)	5857(1)
CB(10)	5697(2)	6569(2)	6178(1)
OB(11)	7998(2)	6271(2)	5994(1)
CB(12)	6641(3)	8978(3)	6140(1)
CB(13)	4214(3)	8571(3)	6074(1)
CB(14)	6711(3)	2683(3)	6966(1)

## EXPERIMENTAL

Melting points were taken on a modified Fisher-Johns apparatus equipped with a thermocouple and a digital thermometer (Lauda) and are uncorrected. Infrared spectra were measured with a Nicolet MX-1 Fourier-transform spectrometer. Intensities are reported as s (strong), m (medium), w (weak), and b (broad). Uv spectra were obtained in ethanol on a "UVIKON 810" UV-Kontron spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter equipped with sodium and mercury light sources by using a 1-dm thermostated cell; reported temperatures are uncorrected. The <sup>1</sup>H nmr spectra were recorded with Varian FT-80A (80 MHz) and WH-270 Bruker (270 MHz) Fourier-transform spectrometers. Chemical shifts are expressed as parts per million

Table 4

Anisotropic Temperature Factors (Å<sup>2</sup> x 10<sup>3</sup>)

	U <sub>11</sub>	U <sub>22</sub>	U <sub>33</sub>	U <sub>23</sub>	U <sub>13</sub>	U <sub>12</sub>
NA(1)	17(1)	24(1)	20(1)	-4(1)	7(1)	3(1)
CA(2)	9(1)	29(1)	17(1)	1(1)	0(1)	-2(1)
NA(3)	14(1)	22(1)	19(1)	2(1)	-2(1)	-1(1)
CA(4)	14(1)	19(1)	19(1)	-2(1)	1(1)	1(1)
CA(5)	21(1)	21(1)	20(1)	-4(1)	7(1)	0(1)
CA(6)	31(2)	24(1)	21(1)	-1(1)	7(1)	-4(1)
CA(7)	22(1)	18(1)	26(1)	0(1)	0(1)	-2(1)
CA(8)	13(1)	20(1)	21(1)	-6(1)	-3(1)	0(1)
CA(9)	11(1)	20(1)	18(1)	-4(1)	-1(1)	-1(1)
CA(10)	12(1)	19(1)	17(1)	-3(1)	1(1)	-3(1)
OA(11)	14(1)	21(1)	24(1)	-8(1)	-4(1)	0(1)
CA(12)	15(1)	22(1)	29(1)	-3(1)	-1(1)	0(1)
CA(13)	24(1)	17(1)	26(1)	-4(1)	3(1)	-1(1)
CA(14)	35(2)	22(1)	32(1)	5(1)	0(1)	1(1)
NB(1)	23(1)	16(1)	15(1)	-1(1)	2(1)	0(1)
CB(2)	23(1)	20(1)	15(1)	-2(1)	1(1)	-2(1)
NB(3)	29(1)	16(1)	19(1)	1(1)	0(1)	3(1)
CB(4)	16(1)	20(1)	19(1)	-5(1)	1(1)	1(1)
CB(5)	20(1)	27(1)	18(1)	-4(1)	2(1)	6(1)
CB(6)	27(1)	27(1)	18(1)	-1(1)	5(1)	6(1)
CB(7)	18(1)	23(1)	21(1)	2(1)	1(1)	1(1)
CB(8)	14(1)	18(1)	21(1)	-3(1)	2(1)	-1(1)
CB(9)	12(1)	20(1)	17(1)	-1(1)	0(1)	0(1)
CB(10)	12(1)	19(1)	20(1)	-3(1)	-3(1)	0(1)
OB(11)	13(1)	21(1)	25(1)	-4(1)	0(1)	-1(1)
CB(12)	27(2)	21(1)	32(2)	-5(1)	-4(1)	1(1)
CB(13)	22(1)	28(1)	25(1)	2(1)	0(1)	9(1)
CB(14)	32(2)	27(1)	27(1)	5(1)	9(1)	5(1)

The temperature factor exponent takes the form:  
 $\exp[-2\pi^2(h,a')(h,a')U']$

(ppm) units downfield from the internal standard, tetramethylsilane (TMS), and the coupling constants (J values) are given in Hertz. Coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The <sup>13</sup>C nmr spectra were recorded on a Bruker WH-90 (22.63 MHz) spectrometer. Mass spectra were measured with an Atlas MAT-731 or MAT-CH-4 spectrometer. Microanalyses were performed by Dr. S. Blum at the Microanalytical Laboratory, Hebrew University of Jerusalem.

Enantiomerically pure *R*(+)-pulegone (*R*-2-isopropylidene-5-methylcyclohexanone) (Fluka or Kodak) was freshly distilled. Guanidine hydrochloride was purchased from Fluka. Freshly prepared and recrystallized acetamide hydrochloride [9], mp 164-166° (ethanol), benzamide hydrochloride [10], mp 169° (acetonitrile), and formamide hydrochloride [11] were prepared by standard techniques.

The free bases of guanidine, benzamide, and acetamide were prepared in dry methanol from stoichiometric amounts of the corresponding hydrochlorides and sodium methylate. After complete precipitation (30 minutes) the sodium chloride was filtered off under dry argon, and the solvent was evaporated at room temperature (10-20°) under high vacuum. This usually gave the free base as a white solid or foam. Because of the instability of the free base of formamide, it was prepared *in situ* by the following procedure: An equimolar quantity of formamide hydrochloride was added to a concentrated solution of sodium methylate in a minimum of dry methanol. The solvent required for the subsequent reaction (dry benzene or acetone) was then added, followed by fast filtration of the sodium chloride formed, under a dry inert atmosphere. Precoated silica gel plates with a fluorescent indicator (Merck, DC-Plastikfolien Kieselgel 60 F254) were used for analytical tlc. Preparative tlc was performed with 0.5-mm silica gel plates (Merck).

Table 5

Hydrogen Atom Coordinates ( $\times 10^4$ ) and Isotropic Temperature Factors ( $\text{\AA}^2 \times 10^3$ )

	x/a	y/b	z/c	U
HA(15)	4412(30)	3111(28)	4905(12)	28(8)
HA(16)	4018(24)	1082(22)	5113(10)	15(6)
HA(17)	6904(25)	1767(25)	2984(10)	21(6)
HA(18)	7672(24)	2802(24)	3452(10)	15(6)
HA(19)	6690(26)	4052(24)	2677(11)	20(6)
HA(20)	5326(31)	3429(28)	2772(12)	39(8)
HA(21)	6618(24)	5263(22)	3598(10)	13(6)
HA(22)	4154(25)	3980(23)	3765(10)	13(6)
HA(23)	4770(23)	4987(22)	4241(10)	17(6)
HA(24)	5051(28)	1855(26)	3599(11)	23(7)
HA(25)	6748(32)	4311(31)	4740(13)	47(9)
HA(26)	7532(28)	1268(27)	4751(13)	34(8)
HA(27)	7785(24)	-298(23)	4566(10)	18(6)
HA(28)	8245(28)	925(27)	4135(11)	31(7)
HA(29)	6345(27)	-1361(25)	3789(11)	23(7)
HA(30)	6946(27)	-347(25)	3290(11)	24(7)
HA(31)	5391(32)	-518(30)	3385(12)	38(8)
HA(32)	5576(31)	6379(28)	2751(13)	40(8)
HA(33)	4844(30)	6737(31)	3359(13)	41(9)
HA(34)	4250(32)	5648(31)	2888(12)	41(8)
HB(15)	5995(26)	6841(26)	4553(13)	33(7)
HB(16)	5491(30)	8675(27)	5034(11)	37(8)
HB(17)	6784(28)	6885(25)	6936(11)	22(7)
HB(18)	5215(29)	7042(29)	7058(12)	33(8)
HB(19)	4978(28)	4698(26)	6999(11)	26(7)
HB(20)	6000(28)	4993(24)	7510(11)	30(7)
HB(21)	7715(23)	4465(23)	6851(9)	9(6)
HB(22)	5808(28)	3896(25)	5981(11)	23(7)
HB(23)	7327(24)	3662(22)	5871(10)	12(6)
HB(24)	4859(24)	6135(22)	6095(9)	10(6)
HB(25)	8609(34)	5794(34)	5810(14)	55(10)
HB(26)	7519(29)	8644(25)	6031(11)	24(7)
HB(27)	6547(27)	9110(26)	6587(12)	28(7)
HB(28)	6479(28)	9899(27)	5950(12)	36(8)
HB(29)	3560(29)	7995(28)	5916(13)	37(8)
HB(30)	4085(27)	8618(26)	6514(12)	32(7)
HB(31)	4126(26)	9486(28)	5903(11)	31(7)
HB(32)	7334(32)	2049(31)	6741(12)	42(8)
HB(33)	6865(25)	2646(24)	7413(11)	23(7)
HB(34)	5828(32)	2372(30)	6896(13)	39(8)

Table 6

Bond Lengths ( $\text{\AA}$ )

CA(2)-NA(1)	1.345(4)	CA(9)-NA(1)	1.456(4)
NA(3)-CA(2)	1.287(4)	CA(4)-NA(3)	1.489(4)
CA(10)-CA(4)	1.537(5)	CA(12)-CA(4)	1.533(5)
CA(13)-CA(4)	1.531(5)	CA(6)-CA(5)	1.537(6)
CA(10)-CA(5)	1.529(5)	CA(7)-CA(6)	1.532(6)
CA(8)-CA(7)	1.525(5)	CA(14)-CA(7)	1.517(6)
CA(9)-CA(8)	1.518(5)	CA(10)-CA(9)	1.533(5)
OA(11)-CA(9)	1.419(4)	CB(2)-NB(1)	1.286(4)
CB(9)-NB(1)	1.463(4)	NB(3)-CB(2)	1.334(4)
CB(4)-NB(3)	1.471(4)	CB(10)-CB(4)	1.538(5)
CB(12)-CB(4)	1.525(6)	CB(13)-CB(4)	1.532(6)
CB(6)-CB(5)	1.525(6)	CB(10)-CB(5)	1.528(5)
CB(7)-CB(6)	1.527(6)	CB(8)-CB(7)	1.531(5)
CB(14)-CB(7)	1.533(6)	CB(9)-CB(8)	1.523(5)
CB(10)-CB(9)	1.536(5)	OB(11)-CB(9)	1.434(4)

Table 7

Bond Angles (deg)

CA(9)-NA(1)-CA(2)	123.4(3)	NA(3)-CA(2)-NA(1)	127.5(3)
CA(4)-NA(3)-CA(2)	116.9(3)	CA(10)-CA(4)-NA(3)	109.4(3)
CA(12)-CA(4)-NA(3)	106.9(3)	CA(12)-CA(4)-CA(10)	114.3(3)
CA(13)-CA(4)-NA(3)	106.7(3)	CA(13)-CA(4)-CA(10)	110.2(3)
CA(13)-CA(4)-CA(12)	109.1(3)	CA(10)-CA(5)-CA(6)	109.2(3)
CA(7)-CA(6)-CA(5)	113.6(3)	CA(8)-CA(7)-CA(6)	109.6(3)
CA(14)-CA(7)-CA(6)	110.6(3)	CA(14)-CA(7)-CA(8)	111.9(3)
CA(9)-CA(8)-CA(7)	111.8(3)	CA(8)-CA(9)-NA(1)	109.8(3)
CA(10)-CA(9)-NA(1)	107.2(3)	CA(10)-CA(9)-CA(8)	109.9(3)
OA(11)-CA(9)-NA(1)	110.5(3)	OA(11)-CA(9)-CA(8)	110.2(3)
OA(11)-CA(9)-CA(10)	109.1(3)	CA(5)-CA(10)-CA(4)	117.7(3)
CA(9)-CA(10)-CA(4)	113.4(3)	CA(9)-CA(10)-CA(5)	108.6(3)
CB(9)-NB(1)-CB(2)	115.1(3)	NB(3)-CB(2)-NB(1)	129.1(3)
CB(4)-NB(3)-CB(2)	123.3(3)	CB(10)-CB(4)-NB(3)	107.1(3)
CB(12)-CB(4)-NB(3)	108.5(3)	CB(12)-CB(4)-CB(10)	114.9(3)
CB(13)-CB(4)-NB(3)	107.1(3)	CB(13)-CB(4)-CB(10)	109.5(3)
CB(13)-CB(4)-CB(12)	109.5(3)	CB(10)-CB(5)-CB(6)	111.0(3)
CB(7)-CB(6)-CB(5)	112.1(3)	CB(8)-CB(7)-CB(6)	109.9(3)
CB(14)-CB(7)-CB(6)	111.7(3)	CB(14)-CB(7)-CB(8)	111.2(3)
CB(9)-CB(8)-CB(7)	112.9(3)	CB(8)-CB(9)-NB(1)	108.4(3)
CB(10)-CB(9)-NB(1)	112.0(3)	CB(10)-CB(9)-CB(8)	109.8(3)
OB(11)-CB(9)-NB(1)	109.4(3)	OB(11)-CB(9)-CB(8)	110.5(3)
OB(11)-CB(9)-CB(10)	106.3(3)	CB(5)-CB(10)-CB(4)	114.5(3)
CB(9)-CB(10)-CB(4)	113.7(3)	CB(9)-CB(10)-CB(5)	110.0(3)

Table 8

Hydrogen Bonds ( $\text{\AA}$ )

NB(3)-NA(3a)	2.966
OB(11)-NA(3b)	2.948
NA(1)-OA(11c)	2.733

Key to symmetry operations relating designated atoms to reference atoms at (x,y,z):

- (a)  $x, 1.0 + y, z$   
 (b)  $0.5 + x, 0.5 - z, 1.0 - z$   
 (c)  $x, y, z$

Preparation of *R*(+)-4,4,7-Trimethyl-1,4,5,6,7,8(or 3,4,5,6,7,8)hexahydroquinazolines (**4**). General Procedure.

Under an inert dry atmosphere, a solution of 20 mmoles of freshly distilled *R*(+)pulegon (**1**) in 5 ml of dry benzene was added dropwise (10 min) at room temperature with stirring to a solution of 22 mmoles of amidine (or guanidine) free base in 50 ml of dry benzene. After addition, the flask was equipped with a Dean-Stark trap for azeotropic removal of water and a condenser, and the mixture was boiled for 24 hours. Progress of the reaction was monitored by tlc. The reaction mixture (colorless for **4b** and **4c**; yellow for **4a**) was cooled, and the remaining traces of sodium chloride were filtered off. The clear solution was evaporated under reduced pressure. The resinous semisolid obtained was triturated with dry hexane several times until a solid precipitate formed, which was filtered off and dried in a vacuum desiccator. The yields, melting points, and spectral parameters are given in Tables 1 and 2.

Preparation of (-)-4,4,7-Trimethyl-9-hydroxy-1,4,5,6,7,8,9,10(3,4,5,6,7,8,9,10)octahydroquinazolines (**3**). General Procedure.

A solution of 20 mmoles of freshly distilled *R*(+)pulegone (**1**) in 15 ml of dry acetone was added dropwise (30 minutes) at 0-10° to a solution of 20 mmoles of amidine in 50 ml of dry acetone with magnetic stirring under a dry inert atmosphere. The mixture was then stirred 30 minutes

more, after which the reaction mixture was stirred at room temperature, the course of the reaction being monitored by tlc. A white solid usually began precipitating after the first hour. The white copious precipitate was filtered and washed with dry acetone or diethyl ether. The mother liquor was evaporated to dryness, the crude residue was triturated with a small amount of dry diethyl ether, and the additional portion of undissolved **3** was filtered. The white solids (**3**) were combined, dried, and recrystallized (Tables 1 and 2).

Preparation of Single Crystals of (-)-7R,9S,10S-4,4,7-Trimethyl-9-hydroxy-1,4,5,6,7,8,9,10(3,4,5,6,7,8,9,10)-octahydroquinazoline (**3d**).

When the above general synthesis for **3** was applied to formamidine and pulegone, with 5-fold quantities of starting materials and solvent, no precipitation had occurred after 48 hours at room temperature. However, tlc showed formation of **3d**. The acetone and unreacted pulegone were evaporated under high vacuum (up to 60°/0.03 mm), and 20 ml of dry acetone was added to the viscous residue. White microcrystalline **3d** precipitated: 2.4 g, mp 156-157°,  $[\alpha]_D^{25} -21.4$  (C = 1.13, methanol); <sup>1</sup>H nmr (deuteriochloroform and deuteriodimethylsulfoxide):  $\delta$  6.99 (s, H-2, 1H), 1.23 (s, CH<sub>3</sub>-4, 3H), 1.15 (s, CH<sub>3</sub>-4, 3H), 0.88 (d, CH<sub>3</sub>-6, 3H), 0.84-1.89 (m); 196 (M<sup>+</sup>). The solid was filtered off and washed with 10 ml of acetone. The mother liquor was left to evaporate slowly at room temperature, and in 24 hours 1.2 g of single crystals suitable for x-ray crystallography formed: mp 166-168°,  $[\alpha]_D^{25} -34$  (C = 1.03, methanol); <sup>1</sup>H nmr (deuteriodimethylsulfoxide):  $\delta$  6.75 (s, H-2, 1H), 1.10 (s, CH<sub>3</sub>-4, 3H), 1.03 (s, CH<sub>3</sub>-4, 3H), 0.83 (d, CH<sub>3</sub>-7, 3H), 0.79-1.79 (m); ms: 196 (M<sup>+</sup>). The crystals were filtered, and the filtrate was left for 24 hours, during which less pure single crystals formed: 0.2 g, mp 152-156°,  $[\alpha]_D^{25} -27$  (C = 1.045, methanol); ms: 196 (M<sup>+</sup>). After filtration, slow evaporation (3 days) yielded 0.4 g of microcrystalline precipitate:  $[\alpha]_D^{25} -20$  (C = 1.81, methanol); ms: 196 (M<sup>+</sup>).

#### Crystal Data.

The crystal properties of **3d** are C<sub>11</sub>H<sub>20</sub>N<sub>2</sub>O, M = 196.3, orthorhombic, a = 10.128 (1), b = 9.953(1), c = 22.393(2) Å, V = 2257 Å<sup>3</sup> (by least-squares refinement on diffractometer angles for 25 automatically centered reflections,  $\lambda = 0.71069$  Å), space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, D<sub>x</sub> = 1.16 g cm<sup>-3</sup>, z = 8 (two independent tautomeric molecules in asymmetric unit); temperature 80 K, transparent colorless cubes.

#### Data Collection and Processing.

Crystal data were collected on a CAD4 diffractometer in  $\omega/2\theta$  mode with  $\omega$  scan width = 0.75 + 0.35 tan, constant  $\omega$  scan speed 3.3°/min, graphite monochromatic Mo K $\alpha$  radiation; 2299 reflections were mea-

sured ( $2^\circ < \theta < 27^\circ$ , h, k, l), 2200 unique (merging R = 0.01), giving 2105 with F<sub>o</sub> > 3 $\sigma$ (F<sub>o</sub>).

#### Structure Analysis and Refinement.

Direct methods were followed by full-matrix least-squares refinement, with all nonhydrogen atoms anisotropic and hydrogens (found from a difference Fourier map) isotropic. The weighting scheme  $\omega = [1.012/s^2(F_o) + 0.00055F_o]$  with  $s(F_o)$  from counting statistics gave satisfactory agreement analyses. Final R and R<sub>w</sub> values are 0.037 and 0.037. All calculations were performed with the SHELX-76 package of crystallographic programs [12].

#### Acknowledgement.

This work was supported in part by a grant from The Basic Research Fund of the Israel Academy of Sciences and Humanities. We thank Mr. N. Grinberg for <sup>13</sup>C nmr measurements.

#### REFERENCES AND NOTES

- \* Present address: Research Laboratories, Eastman Kodak Company, Rochester, New York 14650, USA.
- [1] Dihydropyrimidines, part XII. For part XI, see *Isr. J. Chem.*, 000 (1986).
- [2] For reviews see: [a] "Asymmetric Reactions and Progress in Chemistry", E. L. Eliel and S. Otsuka, eds, Am. Chem. Soc., Washington, D.C. 1982. [b] "Asymmetric Synthesis", Vol 2, J. D. Morrison, ed, Academic Press, New York, 1983.
- [3] A. L. Weis, *Synthesis*, 528 (1985); A. L. Weis, F. Frolow, D. Zamir and M. Bernstein, *Heterocycles*, 22, 657 (1984).
- [4] E. L. Eliel, *Tetrahedron*, 30, 1503 (1974).
- [5] B. Hille, *J. Gen. Physiol.*, 59, 599 (1971).
- [6] W. H. Pirkle, J. M. Finn, J. L. Schreimer and B. C. Hamper, *J. Am. Chem. Soc.*, 10, 3964 (1981); I. W. Wainer, C. A. Brunner and T. D. Doyle, *J. Chromatogr.*, 264, 154 (1983); ref [2a], Chapter 18.
- [7] For a review see: A. L. Weis, *Adv. Heterocyclic Chem.*, 38, 1 (1985).
- [8] A. L. Weis, *Tetrahedron Letters*, 23, 449 (1982); A. L. Weis, Z. Porat and Z. Luz, *J. Am. Chem. Soc.*, 106, 8021 (1984).
- [9] *Organic Syntheses*, Vol 1, 2nd Ed, H. Gilman and A. H. Blatt, eds, Wiley, London, 1956, p 5.
- [10] F. C. Schaefer and A. P. Krapcho, *J. Org. Chem.*, 27, 1255 (1962).
- [11] E. C. Taylor and W. E. Erhart, *J. Am. Chem. Soc.*, 82, 3138 (1960).
- [12] E. M. Sheldrick, SHELX-76, Programme for Crystal Structure Determinations, University of Cambridge, 1976.