

2,6-Diarylhexasahydro-4-pyridazinols by
Acid-Catalyzed Cyclization of Benzaldehyde
Aryl-2-(2-propenyl)hydrazones
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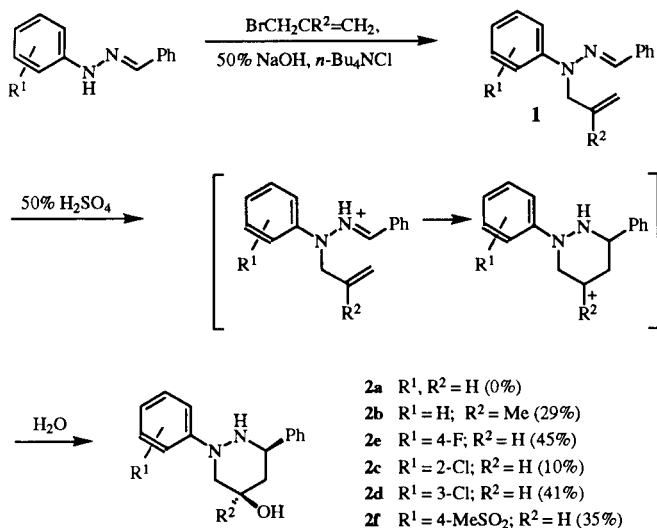
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Treatment of benzaldehyde 1-(2-propenyl)-4-methylsulfonylphenylhydrazone (**1f**) with 45% sulfuric acid gave 2-(4-methylsulfonylphenyl)-6-phenylhexahydro-4-pyridazinol (**2f**) in 35% yield rather than the expected 1-(4-methylsulfonylphenyl)-1-(2-propenyl)hydrazine. The halogen-substituted hydrazones **1c-1e** and benzaldehyde 1-(2-methyl-2-propenyl)phenylhydrazone (**1b**) gave similar results.

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During an intended synthesis of 1-(4-methylsulfonylphenyl)-1-(2-propenyl)hydrazine by the method of Jonczyk, Wlostowska, and Makosza [1,2] we found that treatment of hydrazone **1f** with 45% sulfuric acid resulted in cyclization to the hexahydropyridazinol **2f**



in 35% yield rather than the expected hydrolysis to give the desired hydrazine. The structure of alcohol **2f** was deduced by ¹H nmr spectroscopy and confirmed by X-ray structure determination. A brief and limited study of the scope of this apparently novel cyclization [3] showed that the unsubstituted benzaldehyde phenylhydrazone **1a** gave the normal hydrolysis product, 1-phenyl-1-(2-propenyl)hydrazine, whereas the halosubstituted hydrazones **1c-e** gave the cyclized

products **2c-e** in poor to moderate yields. Similarly, the 2-methyl-2-propenylhydrazone **1b** gave the cyclized product **2b** in 29% yield. The *cis* relationship of the hydroxyl and the 6-phenyl group has been ascertained only for the methylsulfonyl derivative **2f** and the complete absence of the *trans* isomers in the products has not been established. The yields have not been optimized. The reason for the differing behavior of hydrazone **1a** on one side and hydrazones **1b-f** on the other is not clear since both hydrolysis and cyclization are believed to be initiated by protonation of N-2 as shown.

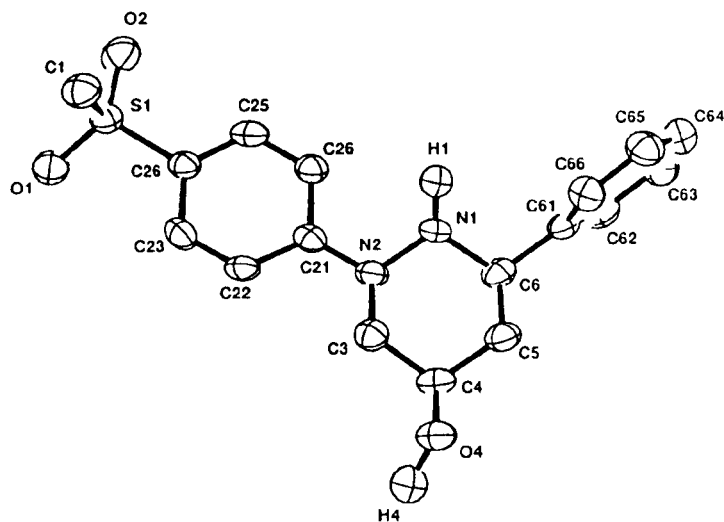


Figure 1. ORTEP drawing of 2-(4-methanesulfonylphenyl)-6-phenylhexahydro-4-pyridazinol (**2f**).

Table I

Fractional Coordinates (X10000) and Isotropic Thermal Parameters				
Atom	X	Y	Z	BISO
S(1)	9182(1)	6939(1)	1552(3)	3.1(1)'
O(1)	8367(3)	7446(3)	565(8)	4.3(1)'
O(2)	10025(3)	6636(3)	-160(8)	4.3(1)'
O(4)	3999(3)	2840(3)	11491(7)	4.0(1)'
N(1)	7057(3)	2772(3)	7268(9)	3.2(1)'
N(2)	6428(4)	3497(3)	6877(8)	2.9(1)'
C(1)	10021(5)	7790(4)	4135(11)	4.0(2)'
C(3)	5593(5)	3647(4)	8889(10)	3.2(2)'
C(4)	4682(4)	2654(4)	9337(10)	3.3(2)'
C(5)	5328(5)	1885(4)	9809(11)	3.4(2)'
C(6)	6197(4)	1778(4)	7606(10)	3.2(2)'
C(21)	7057(4)	4289(4)	5626(9)	2.6(1)'
C(22)	6713(4)	5183(4)	5659(10)	3.0(1)'
C(23)	7319(5)	5962(4)	4336(11)	3.2(2)'
C(25)	8701(4)	5028(4)	2902(10)	3.2(2)'
C(26)	8083(4)	4241(4)	4190(10)	3.1(2)'
C(26)	8335(4)	5885(4)	2939(10)	2.8(1)'
C(61)	6886(4)	1024(4)	7934(10)	2.8(1)'
C(62)	6810(5)	215(4)	6054(10)	3.6(2)'
C(63)	7460(5)	-471(4)	6300(12)	4.3(2)'
C(64)	8183(5)	-350(4)	8457(13)	4.3(2)'
C(65)	8284(5)	436(5)	10350(11)	4.2(2)'
C(66)	7627(5)	1124(4)	10105(11)	3.7(2)'
H(1')	9522	8020	5342	4.0
H(1)	7909	2907	7317	3.1
H(1')	10574	8376	3549	4.0
H(1'')	10501	7477	5008	4.0
H(3)	5182	4114	8484	3.2
H(3')	6037	3939	10473	3.2
H(4)	3184	3011	10949	4.0
H(4')	4179	2398	7818	3.2
H(5)	4775	1229	9898	3.4
H(5')	5803	2095	11371	3.4
H(6)	5689	1535	6101	3.1
H(22)	6072	5269	6688	3.0
H(23)	7054	6551	4325	3.2
H(25)	9391	4987	1982	3.2
H(26)	8367	3659	4186	3.1
H(62)	6315	142	4562	3.6
H(63)	7405	-1018	4958	4.3
H(64)	8612	-829	8631	4.2
H(65)	8776	518	11855	4.1
H(66)	7692	1683	11405	3.6

Table II

Anisotropic Thermal Parameters (Angs X 1000)
 $\exp[-19.739(U11h^2a^*a^*...+2(U12hka^*b^*...))]$

Atom	U11	U22	U33	U12	U13	U23
S(1)	31.7(8)	38.4(8)	44.7(8)	7.9(6)	-1.6(6)	2.9(6)
O(1)	37(2)	51(2)	72(3)	8(2)	-10(2)	16(2)
O(2)	54(2)	49(2)	58(3)	11(2)	16(2)	1(2)
O(4)	33(2)	58(3)	57(2)	13(2)	7(2)	5(2)
N(1)	21(2)	41(3)	61(3)	11(2)	3(2)	11(2)
N(2)	27(2)	40(2)	45(3)	12(2)	3(2)	2(2)
C(1)	41(3)	48(3)	56(4)	7(3)	0(3)	-4(3)
C(3)	35(3)	40(3)	42(3)	9(3)	-3(2)	0(2)
C(4)	25(3)	53(3)	42(3)	7(3)	1(2)	-1(3)
C(5)	29(3)	44(3)	51(3)	5(3)	2(2)	4(3)
C(6)	29(3)	41(3)	44(3)	1(2)	-5(2)	3(2)
C(21)	26(3)	35(3)	35(3)	9(2)	-9(2)	-4(2)
C(22)	27(3)	42(3)	43(3)	12(2)	8(2)	-1(2)

Table II (continued)

Atom	U11	U22	U33	U12	U13	U23
C(23)	38(3)	36(3)	51(3)	18(3)	-4(3)	-2(2)
C(25)	25(3)	49(3)	45(3)	11(3)	2(2)	-1(3)
C(26)	29(3)	37(3)	49(3)	9(3)	-2(2)	1(3)
C(26)	26(3)	33(3)	45(3)	7(2)	-2(2)	-3(2)
C(61)	24(3)	37(3)	41(3)	3(2)	1(2)	6(2)
C(62)	34(3)	45(3)	48(3)	-1(3)	-4(3)	-2(3)
C(63)	52(4)	45(3)	61(4)	14(3)	2(3)	-9(3)
C(64)	47(4)	45(3)	75(4)	15(3)	3(3)	15(3)
C(65)	43(4)	63(4)	56(4)	17(3)	-5(3)	11(3)
C(66)	47(3)	46(3)	45(3)	15(3)	-1(3)	-2(3)

Table III

Interatomic Distances (Å)

S(1)-O(1)	1.462 (4)	C(21)-C(22)	1.405 (7)
S(1)-O(2)	1.450 (4)	C(21)-C(26)	1.427 (7)
S(1)-C(1)	1.760 (6)	C(22)-C(23)	1.371 (7)
S(1)-C(26)	1.744 (5)	C(23)-C(26)	1.416 (7)
O(4)-C(4)	1.428 (6)	C(25)-C(26)	1.371 (7)
N(1)-N(2)	1.436 (5)	C(25)-C(26)	1.370 (7)
N(1)-C(6)	1.471 (6)	C(61)-C(62)	1.381 (7)
N(2)-C(3)	1.476 (7)	C(61)-C(66)	1.397 (7)
N(2)-C(21)	1.369 (6)	C(62)-C(63)	1.393 (8)
C(3)-C(4)	1.509 (7)	C(63)-C(64)	1.374 (8)
C(4)-C(5)	1.512 (7)	C(64)-C(65)	1.358 (8)
C(5)-C(6)	1.563 (7)	C(65)-C(66)	1.400 (7)
C(6)-C(61)	1.513 (7)		

Table IV

Intramolecular Angles (Degrees)

O(1)-S(1)-O(2)	118.7 (3)	N(2)-C(21)-C(26)	121.7 (4)
O(1)-S(1)-C(1)	106.1 (3)	C(3)-C(4)-C(5)	109.7 (4)
O(1)-S(1)-C(26)	109.1 (2)	C(4)-C(5)-C(6)	110.5 (4)
O(2)-S(1)-C(1)	108.0 (2)	C(5)-C(6)-C(61)	114.0 (4)
O(2)-S(1)-C(26)	109.5 (2)	C(22)-C(21)-C(26)	116.7 (5)
C(1)-S(1)-C(26)	104.5 (3)	C(21)-C(22)-C(23)	121.6 (4)
N(2)-N(1)-C(6)	110.6 (3)	C(22)-C(23)-C(26)	120.0 (4)
N(1)-N(2)-C(3)	115.2 (4)	C(26)-C(25)-C(26)	120.5 (5)
N(1)-N(2)-C(21)	114.9 (4)	C(21)-C(26)-C(25)	121.6 (5)
C(3)-N(2)-C(21)	121.1 (4)	C(23)-C(26)-C(25)	119.6 (5)
S(1)-C(26)-C(23)	118.9 (4)	C(6)-C(61)-C(62)	120.4 (5)
S(1)-C(26)-C(25)	121.1 (4)	C(6)-C(61)-C(66)	121.9 (5)
O(4)-C(4)-C(3)	109.0 (4)	C(62)-C(61)-C(66)	117.7 (5)
O(4)-C(4)-C(5)	110.4 (4)	C(61)-C(62)-C(63)	121.1 (5)
N(2)-C(3)-C(4)	112.2 (4)	C(62)-C(63)-C(64)	119.7 (6)
N(1)-C(6)-C(5)	111.5 (4)	C(63)-C(64)-C(65)	121.0 (6)
N(1)-C(6)-C(61)	109.3 (4)	C(64)-C(65)-C(66)	119.3 (5)
N(2)-C(21)-C(22)	121.6 (4)	C(61)-C(66)-C(65)	121.2 (5)

Table V

Intermolecular Distances (Å)	Symmetry Operation Codes
O(2)...C(25) ^b	3.280 (7) a
O(1)...H(4) ^a	1.862 b
	1-X, 1-Y, 1-Z
	2-X, 1-Y, -Z

EXPERIMENTAL

The ¹H (300 MHz) and ¹³C (75 MHz) nmr spectra were determined in deuteriochloroform unless otherwise specified. Melting

points were measured in unsealed capillary tubes and are uncorrected. Mass spectra were obtained by chemical ionization (ammonia or methane) or by electron ionization. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. Magnesium sulfate was used throughout for drying solutions in organic solvents.

Benzaldehyde 1-(2-Propenyl)-4-methylsulfonylphenylhydrazone (1f). General Procedure.

A mixture of 1.86 g (10 mmoles) of 1-(4-methylsulfonylphenyl)hydrazine, 1.06 g (10 mmoles) of benzaldehyde, and 15 ml of ethanol was heated under reflux for 30 minutes, cooled with ice and filtered, and the solids were washed once with cold ethanol and dried to give 2.40 g (88%) of benzaldehyde 4-methylsulfonylphenylhydrazone as a yellow solid, mp 205-206°. ¹H nmr (DMSO-d₆) δ 11.0 (s, 1 H), 8.0 (s, 1 H), 7.7-7.8 (m, 4 H), 7.3-7.5 (m, 3 H), 7.0 (d, J = 8 Hz, 2 H), 3.1 (s, 3 H).

Anal. Calcd. for C₁₄H₁₄N₂O₂S: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.00; H, 5.01; N, 10.11.

A mixture of the hydrazone (2.40 g, 8.8 mmoles), 10 ml of 50% sodium hydroxide, 10 ml of dichloromethane, 1.3 ml (1.82 g, 15 mmoles) of allyl bromide, and 0.1 g (0.35 mmole) of tetra-*n*-butylammonium chloride was stirred at rt for 30 minutes, the layers were separated, and the aqueous layer was extracted twice with dichloromethane. Removal of the solvent from the dried solution gave 2.65 g (96%) of essentially pure title compound **1f**, mp 111-112°; ¹H nmr: δ 7.8 (d, J = 8 Hz, 2 H), 7.7 (d, J = 8 Hz, split further, 2 H), 7.6 (s, 1 H), 7.3-7.5 (m, 5 H), 5.8-6.0 (m, 1 H), 5.3 (d, J = 9 Hz, split further, 1 H), 5.1 (d, J = 14 Hz, 1 H), 4.6 (m, 2 H), 3.0 (s, 3 H).

Anal. Calcd. for C₁₇H₁₈N₂O₂S: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.66; H, 5.78; N, 8.85.

Benzaldehyde 1-(2-Methyl-2-propenyl)phenylhydrazone (1b).

This compound was obtained in 68% yield as an oil, distilling at 210-230° bath temperature/0.003 mm; ¹H nmr: δ 7.7 (d, J = 7 Hz, 2 H), 7.2-7.4 (m, 8 H), 6.9 (m, 1 H), 4.9 (s, 1 H), 4.8 (s, 1 H), 4.4 (s, 2 H), 1.8 (s, 3 H); ms: (LR) Calcd. for C₁₇H₁₉N₂⁺: 251. Found: 251.

Benzaldehyde 1-(2-Propenyl)-2-chlorophenylhydrazone (1c).

This compound was obtained in 80% yield as an oil, distilling at 180-200° bath temperature/0.003 mm; ¹H nmr: δ 7.6 (d, J = 7 Hz, 2 H), 7.1-7.5 (m, 8 H), 5.9-6.1 (m, 1 H), 5.3 (d/d, J = 16/1 Hz, 1 H), 5.2 (d/d, J = 8/1 Hz, 1 H), 4.4 (d/d, J = 5/1 Hz, 2 H); ms: (LR) Calcd. for C₁₆H₁₆ClN₂⁺: 271. Found: 271.

Benzaldehyde 1-(2-Propenyl)-3-chlorophenylhydrazone (1d).

The compound was obtained in 80% yield as an oil, distilling at 215-240° bath temperature/0.003 mm; ¹H nmr: δ 7.7 (d, J = 7 Hz, 2 H), 7.2-7.5 (m, 7 H), 6.9 (d/t, J = 7/1 Hz, 1 H), 5.8-6.0 (m, 1 H), 5.2 (d/d, J = 8/1 Hz, 1 H), 5.1 (d/d, J = 15/1 Hz, 1 H), 4.5 (d, J = 3 Hz, split further, 2 H); ms: (LR) Calcd. for C₁₆H₁₆ClN₂⁺: 271. Found: 271.

Benzaldehyde 1-(2-Propenyl)-4-fluorophenylhydrazone (1e).

The compound was obtained in 61% yield as an oil, distilling at 210-230° bath temperature/0.003 mm; ¹H nmr: δ 7.6 (d, J = 7 Hz, split further, 2 H), 7.2-7.4 (m, 6 H), 7.0 (t, J = 7 Hz, 2 H), 5.8-6.0 (m, 1 H), 5.2 (d/d, J = 8/1 Hz, 1 H), 5.1 (d/d, J = 15/1 Hz, 1 H), 4.5 (d, J = 3 Hz, split further, 2 H); ms: (LR) Calcd. for C₁₆H₁₅FN₂⁺: 255. Found: 255.

2-(4-Methylsulfonylphenyl)-6-phenylhexahydro-4-pyridazinol (2f). General Procedure.

A mixture of hydrazone **1f** (2.60 g, 8.3 mmoles), 20 ml of toluene, and 2.2 ml of 45% sulfuric acid was stirred at rt for 30 hours, diluted with water, and made basic with sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate and the dried organic phases were concentrated to 15 ml, cooled, and filtered. The solid was crystallized from ethyl acetate to give 0.95 g (35% yield, 53% conversion) of the title compound, mp 176-178°. The mother liquor (0.9 g after removal of the solvent) contained mostly unreacted starting material. The crystal for the X-ray structure determination was grown from ethyl acetate. ¹H nmr (DMSO-d₆): δ 7.6 (d, J = 9 Hz, 2 H), 7.3-7.5 (m, 5 H), 7.2 (d, J = 9 Hz, 2 H), 5.2 (d, J = 4 Hz, 1 H, exchangeable with trifluoroacetic acid), 4.8 (d, J = 12 Hz, 1 H, exchangeable with trifluoroacetic acid), 4.2 (d/d, J = 13/4 Hz, 1 H), 3.6-3.8 (m, 2 H), 3.1 (s, 3 H), 2.9 (t, J = 12 Hz, 1 H), 2.2 (d, J = 12 Hz, split further, 1 H), 1.6 (q, J = 11 Hz, probably d/t, J = 11/11 Hz, 1 H); ¹³C nmr (DMSO-d₆): δ 41.7, 44.7, 53.5, 57.8, 64.4, 112.2, 127.3, 127.6, 127.6, 128.7, 129.1, 141.4, 153.8. ir (potassium bromide) 3500 (sharp, m), 1594 (s) cm⁻¹.

Anal. Calcd. for C₁₇H₂₀N₂O₃S: C, 61.42; H, 6.06; N, 8.43. Found: C, 61.48; H, 6.00; N, 8.34.

The crystal data are: C₁₇H₂₀N₂O₃S, from ethyl acetate, colorless, flat plate, -0.05 x 0.08 x 0.50 mm, triclinic, P1 (No. 2), a = 11.603(8), b = 13.818(10), c = 5.273(4) Å, α = 97.15(4), β = 90.19(4), γ = 107.25(4)°, T = -32°, V = 800.4 Å³, Z = 2, FW = 332.42, D_c = 1.379 g/cc, μ(Mo) = 2.09 cm⁻¹.

Data collection was obtained as follows: Rigaku RU300, R-Axis image plate area detector, MoKα radiation, filament size = .5 mm x 1.0 cm, anode power = 55 Kv x 260 ma, crystal to plate distance = 90.0 mm, 105 μ pixel raster, number of frames = 30, oscillation range = 6.0°/frame, exposure = 30.0 min/frame, box sum integration, 3066 data collected, 3.7° ≤ 2θ ≤ 47.7°, maximum h, k, l = 12, 15, 5, no absorption correction, 1177 duplicates, 3.3% R-merge, 1336 unique reflections with I ≥ 3.0σ(I). The quality of the data is limited by a slight crystal splitting.

Solution and Refinement.

The structure solved by direct methods (SHELX) in space group P1. The asymmetric unit consists of one molecule in a general position. Hydrogen atoms were idealized with C-H = .95 Å. The hydroxyl hydrogen was observed from a difference map, refinement by full-matrix least squares on F, scattering factors from the International Tables for X-ray Crystallography, Volume IV, including anomalous terms for S, biweight μ [σ²(I) + 0.0009(I)²]^{-1/2} refined anisotropic: all non-hydrogen atoms, fixed atoms: H, 208 parameters, data/parameter ratio = 6.42, R = 0.082, R_w = 0.089, error of fit = 3.32, max Δ/σ = 0.06, largest residual density = 0.39 e/Å³, near S1.

Results.

This analysis confirms the structure and stereochemistry of 2-(4-methylsulfonylphenyl)-6-phenylhexahydro-4-pyridazinol (**2f**) as shown in Figure 1. The asymmetric carbon centers are C4:*R*, C6:*R* (racemate). The molecules in the crystal interact *via* strong O-H...O hydrogen bonding.

2,6-Diphenylhexahydro-4-methyl-4-pyridazinol (2b).

This compound was obtained in 29% yield as the hydrochloride, mp 214-215° (ethanol); ¹H nmr: (free base) δ 7.2-7.5

(m, 9 H), 6.8 (m, 1 H), 4.2 (m, 1 H), 3.7 (d, $J = 11$ Hz, 1 H), 2.8 (d, $J = 11$ Hz, 1 H), 2.7 (m, 1 H), 2.2 (d/d, $J = 12/3$ Hz, 1 H), 1.8 (d/d, 12/10 Hz, 1 H), 1.4 (s, 3 H).

Anal. Calcd. for $C_{17}H_{21}ClN_2O$: C, 66.99; H, 6.94; N, 9.19. Found: C, 66.98; H, 6.85; N, 9.11.

2-(2-Chlorophenyl)-6-phenylhexahydro-4-pyridazinol (**2c**).

This compound was obtained in 10% yield, mp 188-190° (2-propanol); 1H nmr: δ 7.5 (d, $J = 7$ Hz, 2H), 7.2-7.4 (m, 6 H), 7.0 (m, 1 H), 4.3 (m, 2 H), 3.9 (d/d, $J = 11/4$ Hz, 1 H), 2.4-2.6 (m, 3 H), 1.5-1.7 (m, 2 H).

Anal. Calcd. for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.30; H, 6.03 N, 9.42.

2-(3-Chlorophenyl)-6-phenylhexahydro-4-pyridazinol (**2d**).

This compound was obtained in 41% yield; 1H nmr: δ 7.1-7.5 (m, 7 H), 7.0 (d/d, $J = 7/1$ Hz, 1 H), 6.8 (d/d, $J = 7/1$ Hz, 1 H), 4.0-4.2 (m, 3 H), 2.8 (d, $J = 10$ Hz, 1 H), 2.6 (d/d, $J = 10/8$ Hz, 1 H), 2.5 (d/t, $J = 10/3$ Hz, 1 H), 1.8 (d, $J = 3$ Hz, 1 H), 1.6 (d/t, $J = 10/10$ Hz, 1 H). The hydrochloride had mp 218-219° (ethanol).

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O$: C, 59.09; H, 5.58; N, 8.61. Found: C, 58.77; H, 5.55; N, 8.44.

2-(4-Fluorophenyl)-6-phenylhexahydro-4-pyridazinol (**2e**).

This compound was obtained in 45% yield; 1H nmr: δ 7.3-7.5 (m, 5 H), 7.2 (m, 2 H), 7.0 (m, 2 H), 4.0-4.2 (m, 3 H), 2.7 (m, 1 H), 2.5-2.6 (m, 2H), 2.5 (d/t, $J = 10/3$ Hz, 1 H), 1.6 (d/t, $J = 10/10$ Hz, 1 H). The hydrochloride had mp 230-231° (ethanol).

Anal. Calcd. for $C_{16}H_{18}FCIN_2O$: C, 62.24; H, 5.88; N, 9.07. Found: C, 61.93; H, 5.78; N, 8.90.

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