Selective Synthesis of some 5-Hydrazono-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones

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A simple, highly selective transformation of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones **1-3** and **14** with some phenylhydrazines and heterocyclic hydrazines to 5-hydrazono-2*H*-1-benzopyran-2-ones **4-12** and **15-16** is described. Under more severe conditions the hydrazonoquinoline derivative **17** was obtained from the benzopyran derivative **3** and phenylhydrazine.

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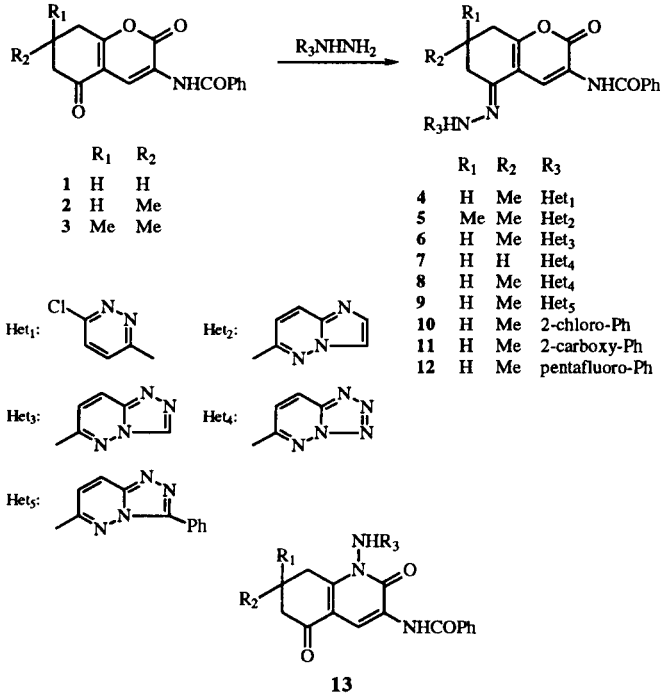
Fused pyran-2-ones are important biologically active compounds and synthons for organic synthesis [1]. Recently, rapid progress has been done in the field of 2*H*-1-benzopyran-2-ones and related quinolinones due to the introduction of several drug-receptor binding models, which enabled a systematic and rational design of novel inhibitors of various enzymes, such as HIV protease [2a] and DNA girase or topoisomerase [2b-c]. 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2-ones possess a wider variety of activities, such as antiarrhytmic, antiinflamatory, anesthetic, analgesic and platelet antiaggregating [3a-b], *etc.* Therefore, an important task of modern organic synthesis is to provide selective transformations, which convert lead compounds into the desired products in high yields.

Recently, we investigated the reactivity of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones **1-3** [4] and some related systems towards nitrogen-containing nucleophiles, which can react either with the lactone ring or with the 5-oxo group. As expected, compounds **1-3** were transformed by the action of ammonia, hydroxylamine, aniline, amino acids, hydrazine and *N,N*-dimethylhydrazine to the corresponding quinoline derivatives [5-7]. On the other hand, hydrazides, phenylhydrazines and heterocyclic hydrazines converted benzopyran-2,5-diones **1-3** selectively into 5-hydrazonobenzopyrans [8-10]. These reactions were carried out in absolute ethanol under the influence of acidic catalysts. The hydrazones, when treated with a mixture of ethanol, water and triethylamine, were selectively converted to the corresponding quinoline-2,5-diones *via* an open-ring intermediate [8]. In the case of a cyclopenta[*b*]pyran-2,5-dione derivative the corresponding fused pyridines were obtained as the only products [10]. Calculated heats of formation of some hydrazone or imine/fused pyridinone product pairs have shown that the obtained products are generally thermodynamically favored over the hypothetical isomers [7,10].

We report here an extension of the selective transformation of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones **1-3** with phenylhydrazines and heterocyclic hydrazines as nitrogen-containing nucleophiles to 5-hydrazonobenzopyrans **4-12** (Scheme 1). The method was also applied to 3-amino derivative **14**, which gave the corresponding hydrazono derivatives **15-16** (Scheme 2). The conversion was carried out in absolute ethanol under the influence of boron trifluoride ethyl etherate or *p*-toluenesulfonic acid. In most experiments, equimolar amounts or 10% excess of the appropriate hydrazine derivative together with up to 40 mol % of the catalyst were used. In the reaction of the compound **14** with phenylhydrazine, three equivalents of the latter were used. Only the reaction of the compound **14** with 3-chloro-6-hydrazinopyridazine was carried out with no catalyst (Table).

Scheme 1



	R_1	R_2
1	H	H
2	H	Me
3	Me	Me

	R_1	R_2	R_3
4	H	Me	Het_1
5	Me	Me	Het_2
6	H	Me	Het_3
7	H	H	Het_4
8	H	Me	Het_4
9	H	Me	Het_5
10	H	Me	2-chloro-Ph
11	H	Me	2-carboxy-Ph
12	H	Me	pentafluoro-Ph

13

We differentiated between the structures of the hydrazone type and the quinoline type on the basis of their infrared and nmr spectroscopic data. The starting com-

Table

Reaction Conditions and Yields of Compounds **4 - 12** and **15-16**

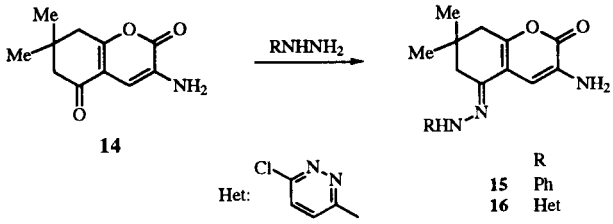
Starting compound	R_3- or R-($NHNH_2$) (mmole)	Catalyst (mmole)	Reflux (h)	Product	Yield (%)
2	Het_1 (1)	A (0.15)	11	**4**	95
3	Het_2 (1.1)	B (0.1)	7	**5**	68
2	Het_3 (1.1)	A (0.4)	5	**6**	86
1	Het_4 (1.1)	B (0.1)	13	**7**	89
2	Het_4 (1.1)	A (0.15)	7.5	**8**	81
2	Het_5 (1)	B (0.1)	5	**9**	83
2	2-chloro-Ph (1)	A (0.4)	7	**10**	82
2	2-carboxy-Ph (1)	A (0.4)	7.5	**11**	88
2	pentafluoro-Ph (1)	A (0.4)	7	**12**	64
14	Ph (3)	B (0.1)	10	**15**	70
14	Het_1 (1)	-	7.5	**16**	68

A: BF_3•Et_2O; B: TsOH.

pounds **1-3** as well as products **4-12** show in their infrared spectra slightly broadened lactone signal with the maximum absorption between 1705 and 1725 cm^{-1}. The ^{13}C nmr spectra of starting materials **1-3** show a typical signal at approximately 194 ppm for C-5, with all other signals appearing at much higher field. In contrast, all hydrazones exhibit no signal at this field. These data are in agreement with those cited for similar compounds [7-11]. In our previous reports we have shown that hydrazones exist as (*E*)-isomers [8,9].

We also wanted to investigate the influence of changes of the 3-amino moiety on the reactivity of such benzopyran-2,5-diones. For this purpose, we performed reactions of the 3-amino derivative **14** [5] with phenylhydrazine and 3-chloro-6-hydrazinopyridazine (Scheme 2). Both

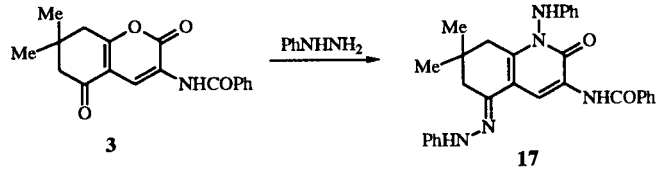
Scheme 2



reactive sites in this system are probably less reactive towards nucleophiles than in compound **3**, since the amino group is a better electron donor than the benzoylamino group. However, compound **14** reacted with both hydrazines and we isolated the corresponding 5-hydrazono derivatives **15** and **16** as the only products. Their structures were confirmed by ^{13}C nmr spectroscopy, where all signals appeared at fields higher than 160 ppm, while in the starting compound **14**, the 5-carbon atom gave a signal at 194.7 ppm. With infrared spectroscopic data, the structure of compound **15** is questionable. In the starting compound **14**, the lactone ring carbonyl band appeared in the ir spectrum at 1710 cm^{-1}, but in the ir spectrum of compound **15**, we assigned the lactone carbonyl band at 1680 cm^{-1}. However, previously mentioned ^{13}C nmr data gave clear evidence as to the structure of compound **15**.

As would be expected, the benzopyran-2,5-diones, when under more drastic conditions, react with nitrogen-containing nucleophiles to form the corresponding hydrazonoquinolinones, as shown in Scheme 3. Thus, heating of compound **3** in boiling phenylhydrazine resulted in the formation of the quinoline derivative **17**.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. Proton and carbon nmr spectra, reported in ppm, were obtained on a Bruker Avance DPX 300 (at 300 and 75.5 MHz) and, if stated so, on a JEOL JNM FX90Q or Varian EM360L spectrometers in dimethyl sulfoxide-d_6 with TMS as an internal standard. Infrared spectra, reported in cm^{-1}, were recorded with a Perkin Elmer 1310 spectrophotometer. Mass spectra, reported in units of m/z, were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Compounds **1-3** [4], **14** [5], 3-chloro-6-hydrazinopyridazine [12a], 6-hydrazinoimidazo[1,2-*b*]pyridazine [12b], 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine [12c], 6-hydrazinotetrazolo-[1,5-*b*]pyridazine [12c] and 6-hydrazino-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine [12d] were prepared as described in the literature. All other compounds were used without purification as obtained from the commercial sources.

General Procedure for the Synthesis of Hydrazone Derivatives **4-12** and **15-16**.

A substituted hydrazine (1-1.1 mmoles; in the case of phenylhydrazine 3 mmoles) was added to the mixture of 1 mmole of the benzopyran **1-3** (or **14**) in absolute ethanol (5 ml), followed by the addition of the appropriate catalyst. The reaction mixture was heated under reflux and upon cooling the products were separated by filtration. Reaction conditions and yields are given in Table.

N-{5-[(6-Chloropyridazin-3-yl)hydrazono]-5,6,7,8-tetrahydro-7-methyl-2-oxo-2*H*-1-benzopyran-3-yl}benzamide (**4**).

This compound was obtained as a yellowish solid, mp 277-280° (from *N*,*N*-dimethylformamide); ^1H nmr: δ 1.07 (d, J = 5.5 Hz, 3H, Me), 2.15 (m, 2H), 2.49 (m, 1H), 2.70 (m, 1H) and 3.06 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 7.54 (m, 4H, 3H of Ph, 4'-H), 7.72 (d, 1H, J = 5.2 Hz, 5'-H), 7.94 (m, 2H, Ph), 8.58 (s, 1H, 4-H), 9.65 (s, 1H, NH), 10.72 (br s, 1H, NH); ir: ν 1658, 1705 cm^{-1}; ms: m/z 423 (M^+, 13), 105 (100).

Anal. Calcd. for $C_{21}H_{18}ClN_5O_3$: C, 59.51; H, 4.28; N, 16.52. Found: C, 59.68; H, 4.33; N, 16.74.

N-{5,6,7,8-Tetrahydro-5-[(imidazo[1,2-*b*]pyridazin-6-yl)hydrazono]-7,7-dimethyl-2-oxo-2*H*-1-benzopyran-3-yl}benzamide (**5**).

This compound was obtained as a yellow solid, mp 269-270° (*N*,*N*-dimethylformamide/methanol); ^{1}H nmr: δ 1.08 (s, 6H, two Me), 2.59 (s, 2H) and 2.61 (s, 2H) (6-CH_2, 8-CH_2), 7.35 (d, 1H, J = 9.8 Hz, 7'-H), 7.59 (m, 4H, 3H of Ph, 2'-H), 7.97 (m, 4H, 2H of Ph, 3'-H, 8'-H), 8.60 (s, 1H, 4-H), 9.66 (br s, 1H, NH), 10.28 (br s, 1H, NH); ^{13}C nmr: δ 27.9, 30.5, 36.6, 39.5, 109.2, 111.5, 116.2, 122.8, 126.1, 126.4, 127.6, 128.5, 131.8, 132.0, 133.5, 136.7, 142.4, 153.0, 157.0, 158.5, 165.8 (21 signals as required; signal at 39.5 was obtained by a DEPT experiment); ir: ν 1650, 1664, 1720 cm^{-1}; ms: m/z 442 (M^+, 40), 105 (100).

Anal. Calcd. for $C_{24}H_{22}N_6O_3$: C, 65.15; H, 5.01; N, 18.99. Found: C, 64.93; H, 5.12; N, 19.18.

N-{5,6,7,8-Tetrahydro-7-methyl-2-oxo-5-[(1,2,4-triazolo-[4,3-*b*]pyridazin-6-yl)hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (**6**).

This compound was obtained as a yellowish solid, mp 301-303° (*N*,*N*-dimethylformamide/methanol); ^{1}H nmr: δ 1.12 (d, 3H, J = 5.6 Hz, Me), 2.17 (m, 2H), 2.55 (m, 1H), 2.74 (m, 1H) and 3.04 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 7.44 (d, 1H, J = 10 Hz, 7'-H), 7.59 (m, 3H, Ph), 7.97 (m, 2H, Ph), 8.20 (d, 1H, J = 10 Hz, 8'-H), 8.54 (s, 1H, 4-H), 9.27 (s, 1H, 3'-H), 9.68 (br s, 1H, NH), 10.48 (br s, 1H, NH); ^{13}C nmr: δ 20.5, 26.6, 31.4, 33.9, 111.7, 114.5, 122.8, 124.7, 126.4, 127.6, 128.5, 132.0, 133.4, 138.3, 142.5, 144.9, 153.4, 158.3, 158.5, 165.7 (20 signals as required); ir: ν 1620, 1665, 1713 cm^{-1}; ms: m/z 429 (M^+, 24), 105 (100).

Anal. Calcd. for $C_{22}H_{19}N_7O_3$: C, 61.53; H, 4.46; N, 22.83. Found: C, 61.13; H, 4.50; N, 22.79.

N-{5,6,7,8-Tetrahydro-2-oxo-5-[(tetrazolo[1,5-*b*]pyridazin-6-yl)hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (**7**).

This compound was obtained as a yellowish solid, mp 315-317° (*N*,*N*-dimethylformamide); ^{1}H nmr: δ 1.98 (m, 2H, 7-CH_2), 2.74 (m, 4H, 6-CH_2, 8-CH_2), 7.58 (m, 3H, Ph), 7.79 (d, 1H, J = 9.8 Hz, 7'-H), 7.98 (m, 2H, Ph), 8.53 (d, 1H, J = 9.8 Hz, 8'-H), 8.62 (s, 1H, 4-H), 9.68 (s, 1H, NH), 10.96 (s, 1H, NH); ^{13}C nmr: δ 19.3, 23.7, 26.3, 111.9, 118.0, 123.0, 124.6, 125.9, 127.6, 128.5, 132.0, 133.5, 140.9, 147.0, 155.1, 158.1, 159.6, 165.7 (18 signals as required); ir: ν 1614, 1655, 1715 cm^{-1}; ms: m/z 416 (M^+, 11), 105 (100).

Anal. Calcd. for $C_{20}H_{16}N_8O_3$: C, 57.69; H, 3.87; N, 26.91. Found: C, 57.52; H, 3.78; N, 27.08.

N-{5,6,7,8-Tetrahydro-7-methyl-2-oxo-5-[(tetrazolo[1,5-*b*]pyridazin-6-yl)hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (**8**).

This compound was obtained as a yellowish solid, mp 288-289° (*N*,*N*-dimethylformamide/ethanol); ^{1}H nmr: δ 1.13 (d, 3H, J = 5.4 Hz, Me), 2.23 (m, 2H), 2.55 (m, 1H), 2.75 (m, 1H) and 3.06 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 7.58 (m, 3H, Ph), 7.77 (d, 1H, J = 9.8 Hz, 7'-H), 7.97 (m, 2H, Ph), 8.52 (d, 1H, J = 9.8 Hz, 8'-H), 8.62 (s, 1H, 4-H), 9.66 (s, 1H, NH), 10.93 (s, 1H, NH); ir: ν 1615, 1675, 1725 cm^{-1}; ms: m/z 430 (M^+, 4), 105 (100).

Anal. Calcd. for $C_{21}H_{18}N_8O_3$: C, 58.60; H, 4.22; N, 26.03. Found: C, 58.81; H, 4.04; N, 26.02.

N-{5,6,7,8-Tetrahydro-7-methyl-2-oxo-5-[(3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (**9**).

This compound was obtained as a yellowish solid, mp 310-312° (*N*,*N*-dimethylformamide); ^{1}H nmr: δ 1.15 (d, 3H, J = 5.5 Hz, Me), 2.20 (m, 2H), 2.53 (m, 1H), 2.75 (m, 1H) and 3.07 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 7.28 (m, 1H, Ph), 7.43 (d, 1H, J = 10 Hz, 7'-H), 7.61 (m, 5H, 2H of Ph, 3H of COPh), 8.01 (m, 2H, COPh), 8.24 (d, 1H, J = 10 Hz, 8'-H), 8.59 (m, 2H, Ph), 8.65 (s, 1H, 4-H), 9.74 (br s, 1H, NH), 10.49 (br s, 1H, NH); ir: ν 1615, 1655, 1708 cm^{-1}; ms: m/z 505 (M^+, 8), 105 (100).

Anal. Calcd. for $C_{28}H_{23}N_7O_3$: C, 66.53; H, 4.59; N, 19.39. Found: C, 66.12; H, 4.62; N, 19.04.

N-{5-[(2-Chlorophenyl)hydrazono]-5,6,7,8-tetrahydro-7-methyl-2-oxo-2*H*-1-benzopyran-3-yl}benzamide (**10**).

This compound was obtained as a brown solid, mp 224-226° (*N*,*N*-dimethylformamide/methanol); ^{1}H nmr: δ 1.12 (d, 3H, J = 5.7 Hz, Me), 2.16 (m, 2H), 2.48 (m, 1H), 2.70 (m, 1H) and 2.95 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 6.85 (deg ddd, 1H, 4'-H), 7.31 (deg ddd, 1H, 5'-H), 7.37 (dd, 1H, J = 7.9 Hz and 1.2 Hz, 3'-H), 7.58 (m, 4H, 3H of COPh, 6'-H), 7.96 (m, 2H, COPh), 8.29 (br s, 1H, NH), 8.67 (s, 1H, 4-H), 9.57 (br s, 1H, NH); ^{13}C nmr: δ 20.6, 26.6, 30.2, 33.8, 112.0, 114.0, 117.3, 120.2, 122.9, 125.2, 127.6, 128.0, 128.5, 129.2, 132.0, 133.5, 141.3, 142.4, 157.1, 158.3, 165.7 (21 signals as required); ir: ν 1665, 1710 cm^{-1}; ms: m/z 421 (M^+, 24), 105 (100).

Anal. Calcd. for $C_{23}H_{20}ClN_3O_3$: C, 65.48; H, 4.78; N, 9.96. Found: C, 65.28; H, 4.57; N, 10.10.

2-{*N*-[(2-Carboxyphenyl)hydrazono]-5,6,7,8-tetrahydro-7-methyl-2-oxo-2*H*-1-benzopyran-3-yl}benzamide (**11**).

This compound was obtained as a brownish solid, mp 288-290° (*N*,*N*-dimethylformamide/methanol); ^{1}H nmr: δ 1.13 (d, 3H, J = 6.3 Hz, Me), 2.07 (m, 2H), 2.48 (m, 1H) and 2.72 (m, 2H) (6-CH_2, 7-H, 8-CH_2), 6.85 (deg dd, 1H, 4'-H), 7.60 (m, 5H, 3H of COPh, 5'-H, 6'-H), 7.87 (dd, J = 7.9 Hz and 1.3 Hz, 3'-H), 7.97 (m, 2H, Ph), 8.69 (s, 1H, 4-H), 9.54 (br s, 1H, NH), 11.21 (br s, 1H, NH), 13.10 (br s, 1H, OH); ^{13}C nmr: δ 20.7, 26.5, 30.5, 33.7, 109.9, 112.0, 112.3, 117.6, 123.0, 125.3, 127.6, 128.5, 131.2, 132.0, 133.5, 134.6, 140.5, 147.1, 156.9, 158.3, 165.7, 169.9 (22 signals as required); ir: ν 1645, 1663, 1715 cm^{-1}; ms: m/z 431 (M^+, 28), 105 (100).

Anal. Calcd. for $C_{24}H_{21}N_3O_5$: C, 66.81; H, 4.91; N, 9.74. Found: C, 66.69; H, 4.75; N, 9.90.

N-{5,6,7,8-Tetrahydro-7-methyl-2-oxo-5-[(pentafluorophenyl)-hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (**12**).

This compound was obtained as a white solid, mp 241-242° (*N*,*N*-dimethylformamide/methanol); ^{1}H nmr: δ 1.12 (d, 3H, J = 5.8 Hz, Me), 2.12 (m, 2H), 2.50 (m, 1H), 2.71 (m, 1H) and 3.03 (m, 1H) (6-CH_2, 7-H, 8-CH_2), 7.57 (m, 3H, Ph), 7.93 (m, 2H, Ph), 8.48 (s, 1H, 4-H), 8.89 (br s, 1H, NH), 9.51 (br s, 1H, NH); ir: ν 1640, 1664, 1708 cm^{-1}; ms: m/z 477 (M^+, 14), 105 (100).

Anal. Calcd. for $C_{23}H_{16}F_5N_3O_3$: C, 57.87; H, 3.38; N, 8.80. Found: C, 57.72; H, 3.28; N, 8.81.

3-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-(phenylhydrazono)-2*H*-1-benzopyran-2-one (**15**).

This compound was obtained as a yellowish solid, mp 225-227° (methanol); ^{1}H nmr (Varian, 60 MHz): δ 1.05 (s, 6H, two Me), 2.39 (s, 2H) and 2.45 (s, 2H) (6-CH_2, 8-CH_2), 5.22 (br s, 2H, NH_2), 6.78 (s, 1H, 4'-H), 7.18 (m, 5H, 4-H, 4H of Ph), 9.27

(br s, 1H, NH); ^{13}C nmr: δ 28.2, 30.5, 36.4, 39.3, 106.6, 112.4, 112.8, 118.6, 128.7, 132.0, 138.0, 146.1, 147.7, 159.7 (14 signals as required); ir: ν 1622, 1680 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.33; H, 6.37; N, 14.12.

3-Amino-5-[(6-chloropyridazin-3-yl)hydrazono]-5,6,7,8-tetrahydro-7,7-dimethyl-2*H*-1-benzopyran-2-one (**16**).

This compound was obtained as a brownish solid, mp 255-256° (methanol); ^1H nmr (Varian, 60 MHz): δ 1.03 (s, 6H, two Me), 2.47 (s, 2H) and 2.53 (s, 2H) (6-CH_2, 8-CH_2), 5.27 (br s, 2H, NH_2), 7.07 (s, 1H, 4-H), 7.68 (dd, 2H, J_{AB} = 10 Hz, 4'-H, 5'-H), 10.68 (br s, 1H, NH); ^{13}C nmr (JEOL, 22.5 MHz): δ 28.0, 30.8, 36.8, 39.5, 106.2, 112.3, 115.8, 129.6, 132.0, 144.5, 147.4, 149.6, 159.4, 159.5 (14 signals as required); ir: ν 1630, 1700 br cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}ClN_5O_2$: C, 53.98; H, 4.83; N, 20.98. Found: C, 53.69; H, 5.01; N, 20.93.

N-[1,2,5,6,7,8-Hexahydro-7,7-dimethyl-2-oxo-1-(phenylamino)-5-(phenylhydrazono)-3-quinolinyl]benzamide (**17**).

A mixture of 1 g (3.22 mmole) of **3** in 4 ml of phenylhydrazine was refluxed for 3 hours. Upon cooling, 8 ml of methanol was added, the separated solid was filtered and washed with methanol to give 650 mg (41%) of **17** as a white solid, mp 225-227°, dec (*N*,*N*-dimethylformamide/methanol); ^1H nmr (Varian, 60 MHz): δ 1.05 (s, 6H, two Me), 2.50 (s, 2H) and 2.56 (s, 2H) (6-CH_2, 8-CH_2), 6.55-7.45 (m, 10H, two Ph), 7.60 (m, 3H, Ph), 8.00 (m, 2H, Ph), 9.18 (br s, 2H, 4-H, NH), 9.37 (br s, 2H, two NH); ir: ν 1630, 1662 cm^{-1}.

Anal. Calcd. for $C_{30}H_{29}N_5O_2$: C, 73.30; H, 5.95; N, 14.25. Found: C, 73.11; H, 6.19; N, 14.31.

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