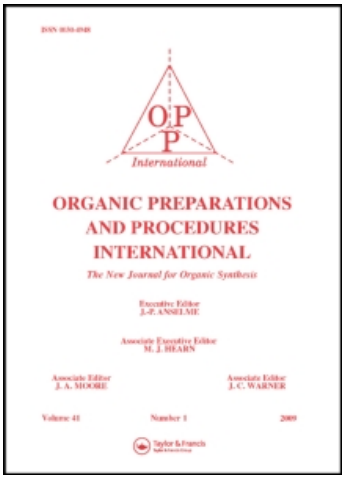

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SYNTHESIS OF SOME TETRAHYDRO-3,3'-BISQUNAZOLIN-4,4'-DIONES

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SYNTHESIS OF SOME TETRAHYDRO-3,3'-BISQUINAZOLIN-4,4'-DIONES†

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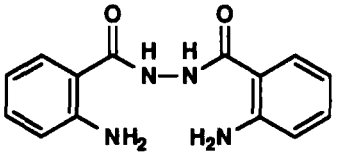
3,3'-Bisquinazolin-4,4'-diones are excellent precursors for nitrogen centered free radicals. 1,2-Bis(2-aminobenzoyl)hydrazine (**1**) provides an easy access to the synthesis of these dimers.[1] We now report the preparation of some new tetrahydro-3,3'-bisquinazolin-4,4'-dione derivatives from **1**.

The reaction of **1** was carried out with a series of ketones in hot methanol containing *p*-toluenesulfonic acid (*p*-TsOH). Acetone, cyclopentanone and cyclohexanone yielded 1:2 products - 2,2,2',2'-tetraalkyl tetrahydro-3,3'-bisquinazolin-4,4'-diones (**2a**, **2j** and **2k**). The UV and IR spectra of **2a**, for example, are similar to those of 2,2-dimethyl-1,2-dihydro-4(1H)-quinazolinone[2] except that **2a** exhibits two carbonyl peaks (1660 and 1635 cm^{-1}) suggesting its bis nature. A singlet at δ 2.53 integrating for twelve protons (4 x CH_3) in the ^1H NMR spectrum favors an azoline structure. If the product was the isomeric 1,2-*bis*(2-isopropylideneaminobenzoyl)-hydrazine, two signals, one each for the *syn* and *anti* methyl protons as in 1,2-diphenyl-1,2-



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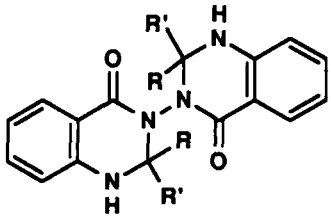

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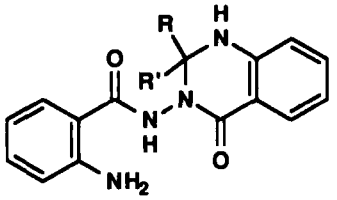

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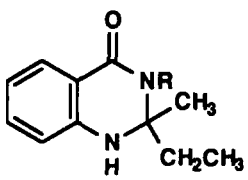

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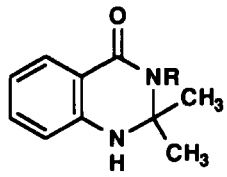

5

a) R = R' = Me b) R = Me, R' = Et c) R = Me, R' = Pr d) R = Me, R' = Pr^i e) R = Me, R' = Ph
f) R = Me, R' = 4-BrPh g) R = Me, R' = 4-O_2NPh h) R = Et, R = Ph i) R = R' = Bz
j) R = R' = $(CH_2)_4$ k) R = R' = $(CH_2)_5$ l) R = R' = $(CH_2)_6$ m) R = R' = $(CH_2)_7$

isopropylideneaminoethane,[3] would be expected.

The reaction of **1** with other ketones yielded 2-amino-N-[2,2'-disubstituted-1,2-dihydro-4-oxo-3(4H)-quinazolinyl] benzamides (**3b-i**, **3l** and **3m**), and attempts to prepare the desired bisquinazolinones from **3** by treatment with excess ketone were unsuccessful. The hydrazine-ketone reaction thus appears to be sensitive to steric variations at C_2. The reaction of **3b** with acetone was carried out in the hope of isolating the unsymmetrical bisquinazolinone, 2-ethyl-2,2',2'-trimethyl-tetrahydro-3,3'-bisquinazolin-4,4'-dione, but the product is **2a**. The same result was obtained with **3c-i**, **3l** and **3m**. A *trans* condensation is evident as acetone replaces the substituent at C_2 during the reaction. By analogy, 2-ethyl-2-methyl-1,2-dihydro-4(1H)-quinazolinone (**4**, R = H)[4] and its N-methyl analogue (**4**, R = CH_3) also underwent a similar *trans* condensation reaction with acetone providing 2,2-dimethyl-1,2-dihydro-4(1H)-quinazolinone (**5**, R=H, CH_3)[2] in high yields. 2-Butanone was isolated from the filtrate as its 2,4-DNP derivative. Attempts to obtain **4** from **5** by refluxing with 2-butanone, however, did not succeed.

A possible mechanism for the conversion of **3b** to **2a** involves the intermediary of **1**. The reaction of a methanolic solution of **3b** (conc. 1.91 x 10^{-5} dm/mol, 50 mL) with acetone (0.3 mL) in the presence of *p*-TsOH (0.1 mg) was monitored by UV. The absorption profile of the reaction mixture changed slowly and became identical to **2a** after 75 min (Table). The characteristic absorption maximum at 333.8 nm of **1** was not evident during the reaction. Hence the hydrazine is not an intermediate in the *trans* condensation reaction. In all probability, the exchange of the reactants is at the Schiff base stage and the exact mechanism is not yet certain. Thermodynamic stability of the products appear to be the driving factor in these *trans* condensation reactions.

TABLE. UV Spectra of the Reaction of **3b** with Acetone in the Presence of *p*-TsOH

	Time (min.)	λ_{max} (MeOH) nm (absorption)
3b	—	217.0(0.96), 247.2 (0.51), 336.6(0.18)
3b + *p*-TsOH	—	221.2(2.08), 246.6 (0.49), 338.4(0.13)
3b + *p*-TsOH + MeCOMe	—	221.0(2.15), 251.2 (0.39), 338.0(0.13)
3b + *p*-TsOH + MeCOMe	5	221.8(2.20), 250.9 (0.38), 339.6(0.13)
3b + *p*-TsOH + MeCOMe	15	221.8(2.26), 250.9 (0.38), 340.4(0.13)
3b + *p*-TsOH + MeCOMe	30	221.8(2.29), 250.9 (0.38), 342.4(0.13)
3b + *p*-TsOH + MeCOMe	45	221.8(2.29), 250.4 (0.35), 342.8(0.13)
3b + *p*-TsOH + MeCOMe	75	222.8(2.30), 250.0 (0.38), 345.0(0.13)
2a	—	227.2(2.27), 250.0 (0.38), 345.0(0.13)
1	—	214.0(2.48), 248.6 (1.03), 333.8(0.56)

EXPERIMENTAL SECTION

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu-435 spectrometer, ^{1}H NMR spectra were obtained on Varian A-60D (90 MHz) and Jeol (80 MHz) spectrometers with TMS as an internal standard. Mass spectra were recorded on Perkin-Elmer Hitachi RMU-6L and MS-30 instruments.

2,2,2',2'-Tetrasubstituted tetrahydro-3,3'-bisquinazolin-4,4'-diones (2).- To a solution of 1,2-bis(2-aminobenzoyl)hydrazine (**1**, 0.54 g, 2 mmol)[1] in methanol (10 mL) containing a small amount of *p*-TsOH, acetone (0.3 mL) was added and the reaction mixture was stirred at room temperature for 15 min. 2,2,2',2'-Tetramethyl tetrahydro-3,3'-bisquinazolin-4,4'-dione (**2a**) separated out as crystalline solid from the homogeneous solution. It was collected, dried and recrystallized from methanol. A similar reaction with cyclopentanone and cyclohexanone, required refluxing for 6 hrs. The corresponding 2,2'-dispirocycloalkane tetrahydro-3,3'-bisquinazolin-4,4'-diones (**2j** and **2k**) separated out from the cooled solution, collected dried and recrystallized from benzene-methanol.

2a: Yield 75%; mp. 272-275°; UV λ_{max} (log ε): 227.8 (4.29), 250 (3.02), 345.6 nm (3.14). IR: 3300 (NH), 1660 (CO), 1635 cm^{-1} (CO) .^{1}H NMR (TFA): δ 2.53 (s, 12H, CH_3), 7.3-8.04 (m, 8H, arom.). MS: m/z 350 (M^+, 12%), 160 (M^+/2-CH_3, 100%).

Anal. Calcd for $C_{20}H_{22}N_4O_2$: C, 68.54; H, 6.33; N, 15.98. Found: C, 68.81; H, 6.56; N, 16.07

2j : Yield 65%; mp. 255-258°; UV λ_{max} (log ε): 216 (4.46), 250 (3.97), 345 nm (3.53). IR: 3320 (NH), 1670 (CO), 1650 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): δ 1.66-2.48 (m, 16H, -CH_2-), 4.54 (b, 2H, NH), 6.66-8.04 (m, 8H, arom.). MS: m/z 402 (M^+, 16%), 201 (M^+/2, 60%), 186 (100%).

Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.61; H, 6.51; N, 13.92. Found: C, 71.82; H, 6.71; N, 14.02

2k : Yield 60%; mp. 260-262°; UV λ_{max} (log ε): 228 (4.16), 250 (3.97), 345 nm (3.53). IR: 3350 (NH), 1680 (CO), 1645 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 1.32-2.06 (m, 20H, -CH_2-), 4.54 (b, 2H, NH), 6.69-7.71 (m, 8H, arom.). MS: m/z 430 (M^+, 18%), 215 (M^+/2, 80%), 69 (C_5H_9, 100%).

Anal. Calcd for $C_{26}H_{30}N_4O_2$: C, 72.53; H, 7.02; N, 13.01. Found: C, 72.47; H, 7.32; N, 12.77

2-Amino-N-[2,2'-disubstituted-1,2-dihydro-4-oxo-3(4H)-quinazolinyl]benzamides (3).- To a solution of **1** (0.54 g, 2 mmol), *p*-TsOH (1 mg) in methanol (10 mL), the appropriate ketone (5 mmol) was added and refluxed for 8 hrs. The excess methanol was distilled off under reduced pressure and 2-amino-N- [2,2'-disubstituted-1,2-dihydro-4-oxo-3(4H)-quinazolinyl]benzamide (**3**) separated from the cooled concentrated solution. It was collected, dried and recrystallized from benzene-methanol.

3b: Yield 62%; mp. 190-192°; UV λ_{max} (log ε): 217.6 (4.25), 247.2 (3.81), 336.6 nm (3.66). IR: 3450 (NH), 3320 and 3250 (NH_2), 1660 (CO), 1640 cm^{-1} CO). ^{1}H NMR (DMSO-d_6): δ 0.88 (t, J = 7 Hz, 3H, H_2C-C$\underline{H}_3$), 1.45 (s, 3H, CH_3), 1.8 (m, 2H, $\underline{H}_2CCH_3$), 5.5 (b, 2H, NH_2), 6.32-7.62 (9H, arom. and NH), 9.9 (s, 1H, amidic NH). MS: m/z 324 (M^+, 7%), 120 (C_7H_6NO, 100%).

Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.64; H, 6.22; N, 17.27. Found: C, 66.79; H, 6.51; N, 17.32

3c : Yield 65%; mp. 185-189°; UV λ_{max} (log ε): 224.2 (4.5), 253 (3.9), 345.5 nm (3.64). IR: 3450

(NH), 3320 and 3250 (NH_2), 1660 (CO), 1640 cm^{-1} (CO).

Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.43; H, 6.55; N, 16.56. Found: C, 67.15; H, 6.45; N, 16.32

3d: Yield 65%; mp. 183-185°; UV λ_{max} (log ε): 224 (4.21), 250 (3.73), 343.3 nm (3.33). IR: 3450 (NH), 3300 and 3250 (NH_2), 1660 (CO), 1640 cm^{-1} (CO).

Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.43; H, 6.55; N, 16.56. Found: C, 67.71; H, 6.59; N, 16.66

3e: Yield 60%; mp. 185-187°; UV λ_{max} (log ε): 225 (4.58), 250 (3.87), 345 nm (3.57). IR: 3410 (NH), 3310 and 3250 (NH_2), 1665 (CO), 1635 cm^{-1} (CO). ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3), 4.8 (s, 1H, NH), 5.45 (b, 2H, NH_2), 6.66-8.04 (m, 8H, arom.), 7.76 (s, 1H, amidic NH). MS: m/z 372 (M^+, 2%), 120(C_7H_6NO, 20%), 78 (C_6H_6, 100%).

Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.94; H, 5.41; N, 15.04. Found: C, 70.81; H, 5.52; N, 15.28

3f: Yield 65%; mp. 189-192°; UV λ_{max} (log ε): 224.5 (4.85), 255 (4. 16), 340.6 nm (3.8). JR: 3430 (NH), 3320 and 3250 (NH_2), 1660 (CO), 1 635 cm^{-1} (CO).

Anal. Calcd for $C_{22}H_{19}BrN_4O_2$: C, 58.54; H, 4.24; N, 12.41. Found: C, 58.64; H,4.28; N, 12.18

3g: Yield 70%; mp. 220-223°; UV λ_{max} (log ε): 222.8 (4. 12), 255.5 (3.8), 345.4 nm (3.01). IR: 3430 (NH), 3320 and 3220 (NH_2), 1660 (CO), 1 635 cm^{-1} (CO).

Anal. Calcd for $C_{22}H_{19}N_5O_4$: C, 63.30; H, 4.59; N, 16.78. Found: C, 63.55; H, 4.70; N, 16.92

3h: Yield 65%; mp. 195-198°; UV λ_{max} (log ε): 224 (4.21), 250 (3.78), 340.4 nm (3.01). IR: 3410 (NH), 3370 and 3250 (NH_2), 1670 (CO), 1635 cm^{-1} (CO).

Anal. Calcd for $C_{23}H_{22}N_4O_2$: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.21; H, 5.91; N, 14.80

3i :Yield 60%; mp. 195-198°; UV λ_{max} (log ε): 210 (4.62), 230 (4.78), 340 nm (4.11). IR: 3450 (NH), 3340 and 3240 (NH_2), 1680 (CO), 1645 cm^{-1} (CO). ^1H NMR ($CDCl_3$): δ 3.25 and 3.5 (ABq, J = 14 Hz, 4H, CH_2), 4.3 (s, 1H, NH), 5.5 (b, 2H, NH_2), 6.5-7.9 (m, 19H, arom. and NH). MS: m/z 462 (M^+, not recorded), 371 (M^+-$PhCH_2$, 2%), 120 (C_7H_6NO, 10%), 32 (100%).

Anal. Calcd for $C_{29}H_{26}N_4O_2$: C, 75.30; H, 5.66; N, 12.11. Found: C, 75.58; H, 5.69; N, 12.30

3l: Yield 55%; mp. 187-190°; UV λ_{max} (log ε): 224.5 (4. 12), 250 (4.01), 342 nm (3.81). IR: 3460 (NH) 3320 and 3250 (NH_2), 1660 (CO), 1640 cm^{-1} (CO).

Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.20; H, 6.64; N, 15.37. Found: C, 69.37; H, 6.42; N, 15.64

3m: Yield 50%; mp. 203-205°; UV λ_{max} (log ε): 223.2 (4.01), 252 (3.62),341.3 nm (3.29). IR: 3460 (NH), 3320 and 3220 (NH_2), 1660 (CO), 1640 cm^{-1} (CO).

Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.81; H, 6.92; N, 14.80. Found: C, 69.98; H, 7.16; N, 14.54

Reaction of 2-Amino-N[-2,2'-disubstituted-1,2-dihydro-4-oxo-3(4H)-quinazolinyl]benzamide (3) with Acetone.- A methanolic solution of **3** (**b-i, l, m**; 2 mmol, 10 mL), acetone (0.3 mL) and *p*-TsOH (1 mg) was kept at room temperature for 0.5 hr with occasional stirring. 2,2,2'2'-Tetramethyl tetrahydro-3,3'-bisquinazolin-4,4'-dione (**2a**) separated out as crystalline solid from the clear solution (in all cases). It was collected and dried. Yield: 60-65%; mp. 272-275°.

Reaction of 2-Ethyl-2-methyl-1,2-dihydro-4(1H)-quinazolinone (4, R = H, CH_3) with Acetone.- A mixture of 2-ethyl-2-methyl-1,2-dihydro-4(1H)-quinazolinone (**4**, 1 mmol),[4] acetone (0.5 mL) and

p-TsOH (1 mg) was refluxed in methanol (10 mL) for 3 hrs. Excess methanol was distilled off under reduced pressure. 2,2-Dimethyl-1,2-dihydro-4(1H)-quinazolinone (**5**)[2] that separated out from the concentrated solution was collected and recrystallized from benzene, yield 60%, **5** (R = H), mp. 182° (lit.[2] mp. 182°); **5** (R = CH_3), mp. 136° (lit.[2] mp. 136°).

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