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SYNTHESIS AND REACTIONS OF 2-(4-PYRIDYL)-7,7-DIMETHYL-5-OXO-5,6,7,8-TETRAHYDROQUINAZOLINE

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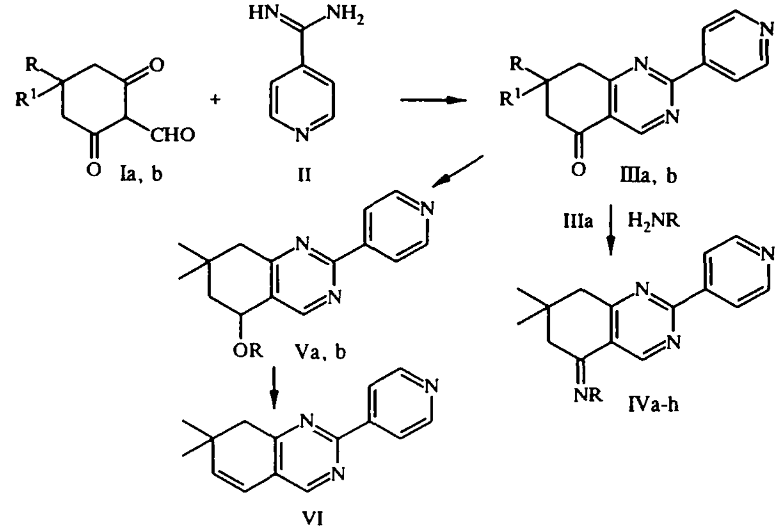
7,7-Dimethyl- and 7-phenyl-2-(4-pyridyl)-5-oxo-5,6,7,8-tetrahydroquinazolines were synthesized in the reactions of 2-formyl-5,5-dimethyl- and 5-phenyl-1,3-cyclohexanediones, respectively, with 4-amidinopyridine. The oxime, thiosemicarbazone, 4-quinazolyl-, nicotinoyl-, isonicotinoyl-, and 2-hydroxybenzoylhydrazones of 2-(4-pyridyl)-5-oxo-7,7-dimethyl-5,6,7,8-tetrahydroquinazoline were obtained. The reduction of this ketone by sodium borohydride leads to the 5-hydroxy derivative.

In a continuation of work on the synthesis of pyrimidines by the reduction of 2-acyl-1,3-cyclanediones with amidines and related 2-aminoazoles [1-5], we obtained 7,7-dimethyl- (IIIa) and 7-phenyl-2-(4-pyridyl)-5-oxo-5,6,7,8-tetrahydroquinazolines (IIIb) in the reactions of 5,5-dimethyl- (IIa) and 5-phenyl-2-formyl-1,3-cyclohexanediones (Ib) with 4-amidinopyridine (II). The oxime (IVa), thiosemicarbazone (IVb), and corresponding hydrazones (IVc-IVh) were obtained in the reactions of IIIa with hydroxylamine, thiosemicarbazide, phenyl- and 4-quinazolylhydrazines, and the hydrazides of salicylic, nicotinic, and isonicotinic acids. The reduction of ketone IIIa by sodium borohydride gives 5-hydroxy derivative Va, which is readily acetylated by acetic anhydride, while dehydration to give 7,8-dihydroxyquinazoline VI occurs upon heating at reflux in 85% orthophosphoric acid.



I, III a R = R¹ = CH_3, b R = C_6H_5, R¹ = H; IV a R = OH, b R = $NHCSNH_2$, c R = NHC_6H_5, d R = NH-quinazol-4-yl, e R = 1-(4-methylpiperazyl), f R = NHCO-pyrid-4-yl g R = NHCO-pyrid-3-yl, h R = $NHCOC_6H_4OH$ (2); V a R = H, b R = $COCH_3$

The structures of these products were supported by PMR and IR spectral data. Thus, the carbonyl band in the IR spectra of acylpyrimidines IIIa and IIIb was found at 1698 and 1694 cm^{-1}. The carbonyl band for the acylhydrazone fragment in IVf-IVh was found at 1665-1668 cm^{-1}. The hydroxyl group in Va gives a broad band at 3440-3160 cm^{-1}, while the carbonyl band of the ester fragment in Vb appears at 1738 cm^{-1}.

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The PMR spectra of these products show pyridine fragment signals at 8.26-8.33 and 8.73-8.80 ppm and a downfield singlet for the $=C_{(4)}H$ proton at 8.4-9.9 ppm. The methylene groups in III and IV were detected at 2.3-2.9 ppm, while the methyl groups at $C_{(7)}$ are equivalent and appear at 1.05-1.15 ppm. The methyl groups at $C_{(7)}$ in V are not magnetically equivalent and appear in the PMR spectra at two singlets of equal intensity. The methylene protons at position 6 are also not equivalent (1.67-1.71 and 2.11-2.17 ppm) and are coupled to each other (J = 12-13 Hz) and with the hydrogen atom at position 5 (4.95 in Va and 6.15 ppm in Vb), giving rise to an ABX spin system. An AX spin system is found for inequivalent protons 5-H and 6-H in the PMR spectrum of VI consisting of two symmetrical doublets with ^3J = 9 Hz.

EXPERIMENTAL

The IR spectra were taken on a Specord 75-IR spectrometer for Vaseline mulls (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The frequencies for the C−H stretching vibrations at 3050-2800 cm^{-1} are not given.

The PMR spectra were taken on a Bruker WH-90/DS spectrometer for solutions in $CDCl_3$ and DMSO-d_6 with TMS as the internal standard.

7,7-Dimethyl- (IIIa) and 7-Phenyl-2-(4-pyridyl)-5-oxo-5,6,7,8-tetrahydroquinazolines (IIIb). A mixture of 0.39 g (2.5 mmoles) hydrochloride salt of 4-amidinopyridine II and 2.5 mmoles of the corresponding 2-formyl-1,3-cyclanedione I with 0.25 ml piperidine in 70 ml methanol was heated at reflux for 5 h. The reaction mixture was left for 24 h in a refrigerator. The crystalline precipitate was filtered off and the filtrate was evaporated to 2/3 of the original volume to give additional IIIa and IIIb.

The yield of **IIIa** was 0.48 g (76%), mp 149-150°C (from ethanol). IR spectrum: 1698, 1605, 1590, 1570, 1545 cm^{-1}. PMR spectrum in $CDCl_3$: 1.16 (6H, s, $2CH_3$), 2.62 (2H, s, CH_2), 2.88 (2H, s, CH_2), 8.35 (2H, m, C_5H_4N), 8.85 (2H, m, C_5H_4N), 9.44 ppm (1H, s, =CH−). Found: C, 71.11; H, 5.98; N, 16.58%. Calculated for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59%.

The yield of **IIIb** was 0.47 g (61%), mp 144-145°C (from ethanol). IR spectrum: 1694, 1598, 1566, 1558, 1538 cm^{-1}. PMR spectrum in $CDCl_3$: 3.02-3.64 (5H, m, $2CH_2$, CH), 7.37 (5H, m, C_6H_5), 8.33 (2H, m, C_5H_4N), 8.82 (2H, m, C_5H_4N), 9.33 ppm (1H, s, =CH−). Found: C, 75.71; H, 5.03; N, 13.95%. Calculated for $C_{19}H_{15}N_3O$: C, 75.72; H, 5.02; N, 13.94%.

5-Hydroxyimino-(IVa), 5-Thiosemicarbazono-(IVb), 5-Phenylhydrazono-(IVc), 5-(4-Quinazolylhydrazono)-(IVd), 5-(4-Methyl-1-piperazyl)imino-(IVe), 5-Isonicotinoylhydrazono-(IVf), 5-Nicotinoylhydrazono-(IVg), and 5-(2-Hydroxybenzoylhydrazono)-2-(4-pyridyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinazolines (IVh). A mixture of 1.25 mmole of the ketone IIIa and 1.25 mmole of the corresponding N-nucleophile (hydroxylamine hydrochloride in the case of IVa) in 10 ml pyridine was heated at reflux for 3.5 h. The precipitate of IV was filtered off. One half of the volume of the remaining solution was evaporated on a rotary evaporator. The concentrated solution was poured onto ice. The precipitate was filtered off and combined with the precipitate formed upon heating at reflux. The combined precipitate was recrystallized from ethanol except for nicotinoylhydrazone IVg, which was recrystallized from toluene.

The yield of IVa was 0.11 g (66%), mp 238-239°C. IR spectrum: 1608, 1575, 1548, 1505, 2800-2620 cm^{-1}. PMR spectrum in DMSO-d_6: 1.04 (6H, s, $2CH_3$), 2.64 (2H, s, CH_2), 2.88 (2H, s, CH_2), 8.29 (2H, center m, C_5H_4N), 8.82 (2H, m, C_5H_4N), 9.36 (1H, s, =CH−), 11.84 ppm (1H, s, OH). Found: C, 63.48; H, 5.69; N, 19.92%. Calculated for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.70%.

The yield of IVb was 0.29 g (71%), mp 240-241°C. IR spectrum: 1600, 1559, 1530, 3424, 3260, 3200, 3120, 3057 cm^{-1}. PMR spectrum in DMSO-d_6: 1.01 (6H, s, $2CH_3$), 2.72 (2H, s, CH_2), 2.88 (2H, s, CH_2), 8.26 (2H, m, C_5H_4N), 8.40 (2H, br.s, NH_2), 8.78 (2H, m, C_5H_4N), 9.82 (1H, s, =CH−), 10.48 ppm (1H, br.s, NH). Found: C, 58.73; H, 5.48; N, 25.64%. Calculated for $C_{16}H_{18}N_6S$: C, 58.87; H, 5.56; N, 25.74%.

The yield of IVc was 0.42 g (98%), mp 224-225°C. IR spectrum: 1645, 1605; 1538, 3250 cm^{-1}. PMR spectrum in $CDCl_3$: 1.13 (6H, s, $2CH_3$), 2.44 (2H, s, CH_2), 2.87 (2H, s, CH_2), 6.89-7.44 (5H, center m, C_6H_5), 7.67 (1H, br.s, NH), 8.31 (2H, m, C_5H_4N), 8.80 (2H, m, C_5H_4N), 9.51 ppm (1H, s, =CH−). Found: C, 73.39; H, 6.06; N, 20.31%. Calculated for $C_{21}H_{21}N_5$: C, 73.44; H, 6.16; N, 20.39%.

The yield of IVd was 0.32 g (65%), mp 264-265°C. IR spectrum: 1620, 1605, 1596, 1580, 1520, 3380, 3050 cm^{-1}. PMR spectrum in DMSO-d_6: 1.05 (6H, s, $2CH_3$), 2.91 (2H, s, CH_2), 3.04 (2H, s, CH_2), 7.48-8.88 (9H, m, C_6H_4, C_5H_4N, =CH), 9.93 (1H, s, =CH−), 11.89 ppm (1H, br.s, NH). Found: C, 69.81; H, 5.35; N, 24.74%. Calculated for $C_{23}H_{21}N_7$: C, 69.86; H, 5.35; N, 24.79%.

The yield of IVe was 0.32 g (73%), mp 120-122°C. IR spectrum: 1598, 1556, 1535, 1528 cm^{-1}. PMR spectrum in $CDCl_3$: 1.09 (6H, s, $2CH_3$), 2.38 (3H, s, CH_3), 2.54-3.06 (8H, m, piperazine), 2.64 (2H, s, CH_2), 2.87 (2H, s, CH_2), 8.33 (2H, m, C_5H_4N), 8.78 (2H, m, C_5H_4N), 9.46 ppm (1H, s, =CH−). Found: C, 68.52; H, 7.49; N, 24.01%. Calculated for $C_{20}H_{26}N_6$: C, 68.54; H, 7.48; N, 23.98%.

The yield of IVf was 0.40 g (86%), mp 200-202°C. IR spectrum: 1665, 1650, 1565, 1548, 1530, 3300, 3190, 3100 cm^{-1}. PMR spectrum in $CDCl_3$: 1.04 (6H, s, $2CH_3$), 2.76 (2H, s, CH_2), 2.96 (2H, s, CH_2), 7.82 (2H, m, C_5H_4N), 8.31 (2H, m, C_5H_4N), 8.80 (4H, m, C_5H_4N), 9.44 (1H, br.s, =CH−), 11.40 ppm (1H, br.s, NH). Found: C, 67.67; H, 5.38; N, 22.44%. Calculated for $C_{21}H_{20}N_6O$: C, 67.73; H, 5.41; N, 22.57%.

The yield of IVg was 0.39 g (84%), mp 179-180°C. IR spectrum: 1680, 1610, 1594, 1584, 1566, 1556, 1534, 3220-3180 cm^{-1}. PMR spectrum in $CDCl_3$: 1.12 (2H, s, CH_2), 2.93 (2H, s, CH_2), 7.32 (1H, m, C_5H_4N), 8.31 (3H, m, C_5H_4N), 8.78 (3H, m, C_5H_4N), 9.18 (1H, m, C_5H_4N), 9.58 (1H, br.s, =CH−), 10.69 ppm (1H, NH). Found: C, 67.77; H, 5.46; N, 22.68%. Calculated for $C_{21}H_{20}N_6O$: C, 67.73; H, 5.41; N, 22.57%.

The yield of IVh was 0.37 g (97%), mp 214-215°C. IR spectrum: 1668, 1598, 1580, 1544, 3360, 3270 cm^{-1}. PMR spectrum in DMSO-d_6: 1.08 (6H, s, $2CH_3$), 2.67 (2H, s, CH_2), 2.96 (2H, s, CH_2), 7.05-8.06 (4H, m, C_6H_4), 8.31 (2H, m, C_5H_4N), 8.84 (2H, m, C_5H_4N), 9.55 (1H, s, =CH−), 11.53 ppm (2H, br.s, OH, NH). Found: C, 68.01; H, 5.62; N, 17.92%. Calculated for $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08%.

2-(4-Pyridyl)-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinazoline (Va). A sample of 0.08 g (2 mmoles) $NaBH_4$ was added to 0.31 g (1.25 mmole) IIIa in a mixture of 30 ml ethanol and 3 ml water and left for 72 h at 20°C. Then, two-thirds of the ethanol was distilled off and the reaction mixture was poured onto ice to give 0.20 g (68%) Va, mp 134-135°C. IR spectrum: 1668, 1610, 1550, 3440-3160 cm^{-1}. PMR spectrum in $CDCl_3$: 1.05 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.67 (1H, d.d, $^3J_{AX} = 10$, $^2J_{AB} = 12$ Hz, $C_{(6)}H$), 1.75 (1H, OH), 2.11 (1H, d.d, $^3J_{BX} = 6$, $^2J_{AB} = 12$ Hz, $C_{(6)}H$), 2.82 (2H, s, CH_2), 4.93 (1H, d.d, $^3J_{BX} = 6$, $^3J_{AX} = 10$ Hz, $C_{(5)}H$), 8.33 (2H, m, C_5H_4N), 8.73 (2H, m, C_5H_4N), 9.04 ppm (1H, =CH−). Found: C, 70.56; H, 6.73; N, 16.49%. Calculated for $C_{15}H_{17}N_3O$: C, 70.57; H, 6.71; N, 16.46%.

2-(4-Pyridyl)-5-acetoxy-7,7-dimethyl-5,6,7,8-tetrahydroquinazoline (Vb). A sample of 0.24 g (1.0 mmole) Va in 10 ml acetic anhydride was heated at reflux. After cooling, the mixture was poured into water, brought to pH ~5 by adding sodium bicarbonate, and extracted with chloroform until the aqueous layer was completely colorless. The combined extracts were dried over Na_2SO_4 and chloroform was distilled off. A drop of water was added to the oil obtained and left for 48 h to give 0.18 g (65%) Vb, mp 88-90°C. IR spectrum: 1738, 1654, 1600, 1582, 1544 cm^{-1}. PMR spectrum in $CDCl_3$: 1.06 (3H, s, CH_3), 1.17 (3H, s, CH_3), 2.17 (3H, s, CH_3), 1.73 (1H, d.d., $^3J_{AX} = 8$, $^2J_{AB} = 13$ Hz, $C_{(6)}H$), 2.15 (1H, d.d, $^3J_{BX} = 6$, $^2J_{AB} = 13$ Hz, $C_{(6)}H$), 2.84 (2H, s, CH_2), 6.15 (1H, d.d, $^3J_{AX} = 8$, $^3J_{BX} = 6$ Hz, $C_{(5)}H$), 8.29 (2H, m, C_5H_4N), 8.78 ppm (3H, m, C_5H_4N, =CH−). Found: C, 68.66; H, 6.49; N, 14.16%. Calculated for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13%.

2-(4-Pyridyl)-7,7-dimethyl-7,8-dihydroquinazoline (VI). A sample of 0.15 g (0.6 mmole) Va in 6 ml 85% phosphoric acid was heated at reflux for 3.5 h. After cooling, the mixture was poured onto ice and brought to pH 4-5 by adding sodium bicarbonate. After 1 h, the precipitate was filtered off to give 0.09 g (64%) VI, mp 61-62°C. IR spectrum: 1636, 1600, 1576, 1526 cm^{-1}. PMR spectrum in $CDCl_3$: 1.13 (6H, s, $2CH_3$), 2.91 (2H, s, CH_2), 6.00 (1H, d, $J_{AX} = 9$ Hz, $=C_{(6)}H-$), 6.38 (1H, d, $J_{AX} = 9$ Hz, $=C_{(5)}H-$), 8.31 (2H, m, C_5H_4N), 8.40 (1H, s, $=C_{(4)}H-$), 8.73 ppm (2H, m, C_5H_4N). Found: C, 75.99; H, 6.32; N, 17.82%. Calculated for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71%.

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