

The Synthesis and Spectroscopic Properties of
3-(2',4'-Xylyl)-1*H*,3*H*-quinazoline-2,4-diones

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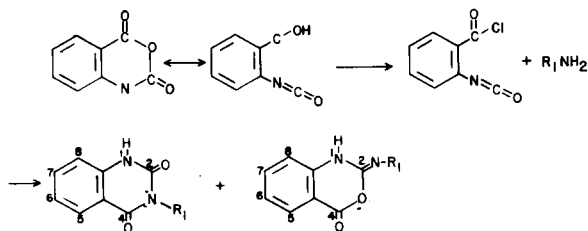
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The synthesis of 3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-diones (**1a**, **9a-j**) has been accomplished. Their pmr and ir spectra data for all compounds are presented.

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Our interest in the preparation of 1*H*,3*H*-quinazoline-2,4-diones (**1a,b**) prompts us to report some of our findings in a related series, namely 3-(2',4'-xylyl)-(1*H*,3*H*)-quinazoline-2,4-diones which have various substituents, e.g., **1a**, **9a-j**.

Among the methods (**2a-d**) reported for the preparation of 3-substituted 1*H*,3*H*-quinazoline-2,4-diones the following synthetic sequence, that we found to be the most satisfactory (**2c**), was adopted to generate compound **1a** (Scheme 1).



The scheme starts with commercially available isatoic anhydride (**2**) which on treatment with thionyl chloride gives the chloro derivative **4**. Addition of equimolar proportions of 2,4-dimethylaniline (**5a**) to a solution of **4** in toluene gives a mixture of the quinazolinone **1a** (insoluble in the medium) and benzoxazinone (**6a**). These were separated by filtration. Iwakura, *et al.*, (**3**) obtained **1b** when aniline (**5b**) is used instead of **5a**. The relative proportions of **1a** and **6a** obtained are greatly affected by the experimental conditions. They are: (a) 1:0, if to a solution of **4** (0.110 mole) in 200 ml. of toluene, a mixture of **5a** (0.110 mole) and tri-*n*-butylamine in 130 ml. of toluene is added dropwise at 0° , the reaction mixture stirred at this temperature for one hour and for twelve hours at room temperature and again for seven hours at 100° ; (b) 1:1, if the previous technique is used

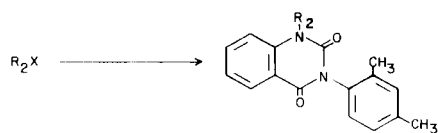
but with a more diluted solution (620 ml.) of the toluene medium; (c) 1:3, if the experimental conditions differ from the case 1:0 only by the fact that after one hour of stirring at 0° , the reaction mixture is allowed to stand without stirring at room temperature overnight and afterwards is heated with stirring at 100° for seven hours.

The conversion of **6a** to **1a** is carried out in polyphosphoric acid medium (**4**).

Compounds **1a** and **6a** are characterized by standard methods. In particular, the infrared spectrum of **1a** shows the characteristic bands of quinazolinone systems (**5**) in the range 1489-1509, 1594-1615 and $758\text{-}765\text{ cm}^{-1}$ and the absorption bands of carbonyl groups at C_2 and C_4 , respectively, at 1660 and 1710 cm^{-1} (Table I). The fact that the carbonyl bands are well resolved is consistent with a monosubstituted benzouracil at position 3 (**1b**). This data does not allow the hypothesis of a Chapman rearrangement (**6**) and the formation of a monosubstituted 1*H*,3*H*-quinazoline-2,4-dione at position 1 (**1b**). Furthermore, the pmr spectrum (deuteriochloroform) is in agreement with structure **1a** (Table II). We found the two methyl singlets at δ 8.10 and 6.61 and observed a downfield signal (δ 8.2) for the proton at atom C_5 , *peri* to the carbonyl group at atom C_4 . Furthermore, a signal of the proton at carbon atom C_7 was observed at δ 7.65. The signals of the other aromatic protons which are clustered in an unresolvable system δ (7.1-7.5) were noted, as well as an upfield signal (δ 6.75) for the proton (H_8) at carbon atom C_8 . This latter proton appears at δ 7.18 in the 1*H*,3*H*-quinazoline-2,4-dione (**7**) spectrum (Table I). The presence of an aromatic group at position 3 affects the $\text{N}_1\text{-H}$ band character. On the contrary, the peak position of (H_8) of compounds **9a-j** is the same as that of (H_8) in the spectrum of **7**. It can be pointed out that the (H_8) upfield shift of the derivative **1a** is less important than that

of (H_g) in 1-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (1*b*) in comparison with the position of this proton in the spectrum of 7. The structural assignment of 6*a* is consistent with its infrared spectrum by the position of the carbonyl absorption at 1745 cm⁻¹ and by the relative absorption intensity of the -C≡N and C=O group bands (4). The features of the aromatic proton signals of the compounds 1*a* (in deuteriochloroform) and 6*a* (in DMSO) are quite similar. In the latter compound the (H_g) proton resonance peak appears in the unresolved multiplet (δ 7.1-7.5). The singlet at δ 2.21 attributed to the two methyl groups.

The alkylation reaction of 1*a* by different halogen derivatives 8*a-j* are carried out with methanolic sodium hydroxide or with sodium hydride in dimethylformamide as solvent. Methods one and two are employed when 1*a* is treated with 8*a* and 8*b-j* respectively, (Scheme 2). Table I, lists the various quinazolinodiones 9 so obtained which have not been described in the literature. As can be seen



in Tables I and II, the ir and nmr spectra support (1*b*) the assigned structures for compounds 9*a-j*. Compounds 1*a* and 9*a-j* were screened for antiinflammatory and analgesic properties.

Table I

Physical Properties of 3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione 1*a* and 9*a-j*.

Compound	M.p. °C (a)	Yield (%)	Rf (b)	Ir λ (cm ⁻¹)
1 <i>a</i>	221	90	0.68 (c)	1727-1670
9 <i>a</i>	182	85	0.29	1715-1670
9 <i>b</i>	114	69	0.41	1712-1665
9 <i>c</i>	156	62	0.54	1710-1665
9 <i>d</i>	145	90	0.46	1715-1670
9 <i>e</i>	108	49	0.55	1712-1665
9 <i>f</i>	88	59	0.67	1710-1660
9 <i>g</i>	89	51	0.70	1700-1650
9 <i>h</i>	164	80	0.53	1715-1670
9 <i>i</i>	160	70	0.61	1720-1670
9 <i>j</i>	155	62	0.56	1718-1675 and 1740

(a) melting points. (b) The purity of compounds 1*a* and 9*a-j* was verified by thin layer chromatography (DC-Plastikfolien Kieselgel 60 F 254), eluent ether-ligroin (1:1) or (c) chloroform-ethanol (19:1) and Rf values are indicated just as the carbonyl groups absorption bands positions (λ cm⁻¹) in ir spectra (chloroform) of 1*a* and 9*a-j*.

EXPERIMENTAL

The melting points were determined with a Dr. Tottoli melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 457 ir spectrophotometer. The nmr spectra were measured as chloroform or dimethylformamide solutions, with a Varian model HA 100 nmr spectrometer. The chemical shifts (δ) are expressed as ppm from internal TMS. The chemical formula are indicated when the microanalytical data are good to within ± 0.2%.

o-Isocyanatobenzoyl Chloride (4).

A mixture of 2 (12.3 g.), thionyl chloride (72 g.), pyridine (3 drops) in a nitrogen atmosphere was refluxed for 45 hours. After the solvent was evaporated to dryness under reduced pressure to give a solid to which benzene (50 ml.) was added. By filtration, a filtrate was separated and after evaporation under reduced pressure gave a crude material, which was distilled to give 4 (11.3 g.), b.p. 145-170°/20 mm which failed to give crystalline compound; ir ν max (chloroform): 2300 (N=C=O) cm⁻¹ 1775 and 1735 (C-C=O) cm⁻¹.

3-(2',4'-Xylyl)-1*H*,3*H*-quinazoline-2,4-dione (1*a*).

To a solution of 4 (20 g.) in toluene (200 ml.), a mixture of 5*a* (13.2 g.) and tri-*n*-butylamine (18 g.) in toluene (130 ml.) was added dropwise with stirring at 0° over a period of 15 minutes. The reaction mixture was maintained at this temperature for 1 hour, and then overnight at room temperature. After heating at 100° for 7 hours, and cooling, the solvent was evaporated under reduced pressure and worked up with ethanol-water (1:1) (100 ml.) and filtered. Crystallization from ethanol gave 1*a* (10 g.) m.p. 221°.

Anal. Calcd. for C₁₆H₁₄O₂N₂: C, 72.16; H, 5.30; O, 12.02; N, 10.52. Found: C, 72.06; H, 5.30; O, 12.00; N, 10.49.

1-Methyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (9*a*).

A mixture of 1*a* (5.6 g.), methyl iodide (31.8 ml.) in a solution of sodium hydroxide in methanol 2.8% (59.5 ml.) was refluxed for 3 hours. The solvent was evaporated under reduced pressure and the crude material recrystallized from ethanol yields 9*a*, 85%, m.p. 182-184°.

Anal. Calcd. for C₁₇H₁₆N₂O₂: C, 72.84; H, 5.75; O, 11.42; N, 9.99. Found: C, 72.82; H, 5.72; N, 9.98.

1-Ethyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (9*b*).

A mixture of 1*a* (1.1 g.), sodium hydride (0.24 g.) in dry dimethylformamide (15 ml.) was stirred for 40 minutes at room temperature and under nitrogen atmosphere. After cooling at 0°, a solution of ethyl bromide (1.1 g.) in dry DMF was added dropwise and the dropping funnel was rinsed with an additional 5 ml. of DMF. The reaction mixture was stirred overnight at room temperature. Ice water (100 ml.) was added and the precipitated crystals were collected by filtration, recrystallized from ligroin to yield 9*b*, 69%, m.p. 114-116°.

Anal. Calcd. for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; O, 10.87; N, 9.52. Found: C, 73.42; H, 6.16; N, 9.53.

1-Propyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4 dione, (9*c*).

According to the above procedure, 1*a* (4.6 g.), sodium hydride (1 g.) in dry DMF (63 ml.) was treated with *n*-propyl bromide (5.15 g.). After ice water addition the precipitate was extracted with chloroform. The organic solvents were evaporated under reduced pressure and the crude material was recrystallized from benzene-ligroin (1:1) to yield 9*c*, 62%, m.p. 156-157°.

Table II
Nmr Spectra of 3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-diones, **1a** and **9a-j** in Chloroform as the Solvent

Compounds	R ₁ substituent protons	Chemical Shifts δ (ppm from TMS)				
		Methyl groups of the xylyl group	H ₅	H ₆	H ₇	H ₃
7	11.01	11.23	7.00	7.16	7.63	7.18
1a	11.05	CH ₃ (4'): 2.15 (s) CH ₃ (2'): 2.41 (s)	8.13	M* (7.0-7.4)	M* (7.0-7.4)	6.75
9a	3.62 (s)	CH ₃ (4'): 2.11 (s) CH ₃ (2'): 2.36 (s)	8.25	M* (7.0-7.4)	7.66	M* (7.0-7.4)
9b	CH ₃ : 1.36 (t) CH ₂ : 4.22 (q)	CH ₃ (4'): 2.10 (s) CH ₃ (2'): 2.36 (s)	8.25	M* (7.0-7.35)	7.71	M* (7.0-7.35)
9c	CH ₃ : 1.04 (t) CH ₂ (2'): 1.82 (m) CH ₂ (1'): 4.17 (t)	CH ₃ (4'): 2.10 (s) CH ₃ (2'): 2.36 (s)	8.36	M* (7.0-7.4)	7.65	M* (7.0-7.4)
9d	CH ₂ (1'): 4.75 (dd) CH (2'): 5.82 (m) CH ₂ (3'): 5.35 (dd) 5.15 (dd)	CH ₃ (4'): 2.10 (s) CH ₃ (2'): 2.35 (s)	8.25	M* (7.0-7.3)	7.68	M* (7.0-7.3)
9e	CH ₂ (1'): 4.68 (de) CH (2' and 3'): 5.70 (m) CH ₃ (4'): 1.72 (d)	CH ₃ (4'): 2.15 (s) CH ₃ (2'): 2.41 (s)	8.26	M* (7.0-7.8)	7.64	M* (7.0-7.8)
9f	CH ₂ (2'): 4.18 (t) CH ₂ (2'): 1.46 (m) CH ₃ (5'): 0.92 (t)	CH ₃ (4'): 2.11 (s) CH ₃ (2'): 2.37 (s)	8.22	M* (7.0-7.35)	7.70	M* (7.0-7.35)
9g	CH ₂ (1'): 4.19 (t) CH ₂ (2' to 5'): 1.40 (m) CH ₃ (6'): 0.88 (t)	CH ₃ (4'): 2.12 (s) CH ₃ (2'): 2.37 (s)	8.25	M* (7.1-7.4)	7.65	M* (7.1-7.4)
9h	CH ₂ (1'): 5.40 (J = 17) 5.12 (J = 17)	CH ₃ (4'): 2.15 (s) CH ₃ (2'): 2.36 (s)	8.26	M* (7.1-7.4)	7.58	M* (7.1-7.4)
9i	CH ₂ (1'): 4.26 (J = 17) 5.19 (J = 17)	CH ₃ (4'): 2.15 (s) CH ₃ (2'): 2.36 (s)	8.30	M* (7.0-7.35)	7.52	M* (7.0-7.35)
9j	CH ₃ (4'): 2.42 (s)	CH ₃ (4'): 2.17 (s) CH ₃ (2'): 2.34 (s)	8.28	M* (7.0-7.60)	7.85	M* (7.0-7.60)

(J) - Coupling constants are measured in Hertz. s, t, q, m, d, dd, and de, respectively, mean: singlet, triplet, multiplet, doublet, doublet of doublet, broad doublet. M* Means that the proton peak is in an unresolved system of which the limits are pointed out.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; O, 10.38; N, 9.09. Found: C, 73.99; H, 6.53; N, 9.09.

1-(2',3'-Allyl)-3-(2',4'-xylyl)-1*H*-3*H*-quinazoline-2,4-dione (**9d**).

According to the above procedure, **1a** (2.2 g.), sodium hydride (0.48 g.), in DMF (30 ml.) was treated with allyl bromide (2.42 g.). After water addition and extraction with chloroform the organic solvents were evaporated to yield **9d**, 90%, m.p. 145-146°.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; O, 10.05; N, 8.80. Found: C, 75.43; H, 5.69; N, 8.80.

1-Crotyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9e**).

According to the above procedure, **1a** (4 g.), sodium hydride (0.88 g.) in dry DMF (55 ml.) was treated with crotyl bromide (4.4 g.). After water addition and extraction with chloroform, the crude material obtained was purified by column chromatography (70 g. of 70-230 mesh silica gel, using ether-ligroin (1:1) as eluent) and **9e** was obtained, 49%, m.p. 108°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; O, 9.99; N, 8.74. Found: C, 74.96; H, 6.28; N, 8.72.

1-Pentyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9b**).

According to the above procedure, **1a** (3.5 g.), sodium hydride (0.7 g.) in dry DMF (40 ml.) was treated with pentyl bromide (3.9 g.). After water addition and extraction with chloroform, the crude product was recrystallized from ether-ligroin (1:1) and **9f** was obtained, 59%, m.p. 88°.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; O, 9.51; N, 8.33. Found: C, 74.96; H, 7.19; N, 8.32.

1-Hexyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9g**).

According to the above procedure, **1a** (5.5 g.), sodium hydride (1.2 g.) in dry DMF (65 ml.) was treated with hexyl bromide (6.1 g.). After water addition and extraction with chloroform, the crude product was recrystallized from ethanol yielding **9g**, 51%, m.p. 89°.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; O, 9.13; N, 7.29. Found: C, 75.38; H, 7.48; N, 7.28.

1-Benzyl-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9h**).

According to the above procedure, **1a** (3.3 g.), sodium hydride (0.72 g.) in dry DMF (45 ml.) was treated with benzyl bromide (5.13 g.). After water addition and extraction with chloroform

the crude product was recrystallized from benzene-ligroin (1:1) to yield **9h**, 80%, m.p. 163-164°.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; O, 8.98; N, 7.86. Found: C, 77.49; H, 5.67; N, 7.86.

1-(Methyl-4'-benzyl)-3-(2',4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9i**).

According to the above procedure, **1a** (2.6 g.), sodium hydride (1 g.) in DMF (40 ml.) was treated with benzyl chloride (2.8 g.). After water addition and extraction with chloroform, the crude product was recrystallized from ethanol and yields **9i**, 70%, m.p. 160°.

Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; O, 8.64; N, 7.56. Found: C, 77.80; H, 5.98; N, 7.56.

1-Benzoyl-3-(2,4'-xylyl)-1*H*,3*H*-quinazoline-2,4-dione (**9j**).

According to the above procedure, **1a** (2.5 g.), sodium hydride (0.6 g.) dry DMF (35 ml.) was treated with freshly distilled benzoyl chloride (3.5 g.). After water addition and extraction with chloroform the crude material was purified by column chromatography (100 g. of 70-230 mesh Kieselgel, using chloroform as eluent) and **9j** was obtained, 62%, m.p. 180-181°.

Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; O, 9.03; N, 7.91. Found: C, 77.94; H, 5.12; N, 7.90.

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