

Synthesis of Some Pyrimido[1,2-*c*]quinazolin-4-one Derivatives

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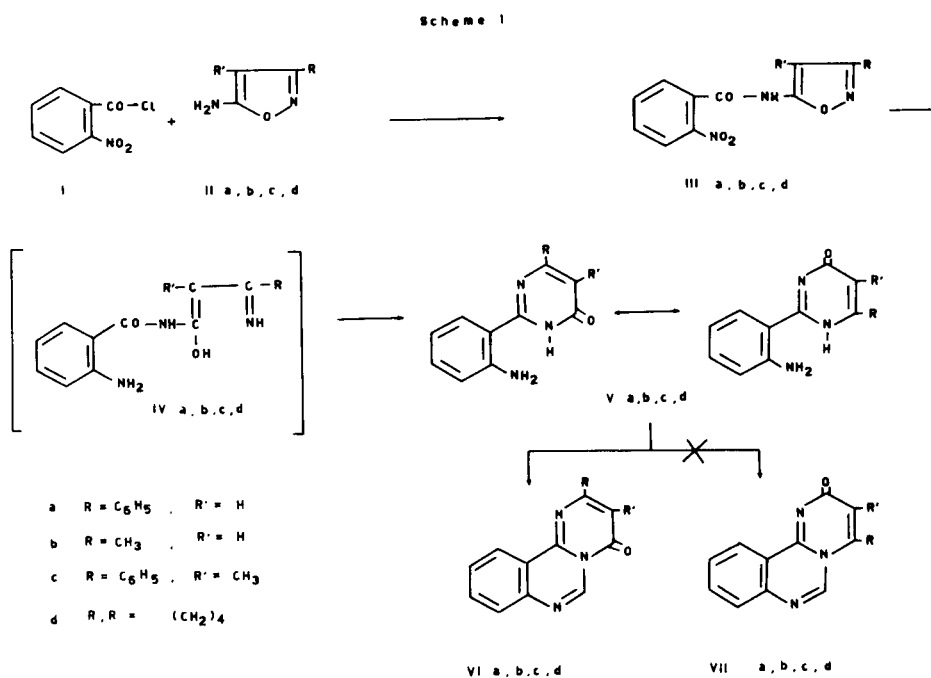
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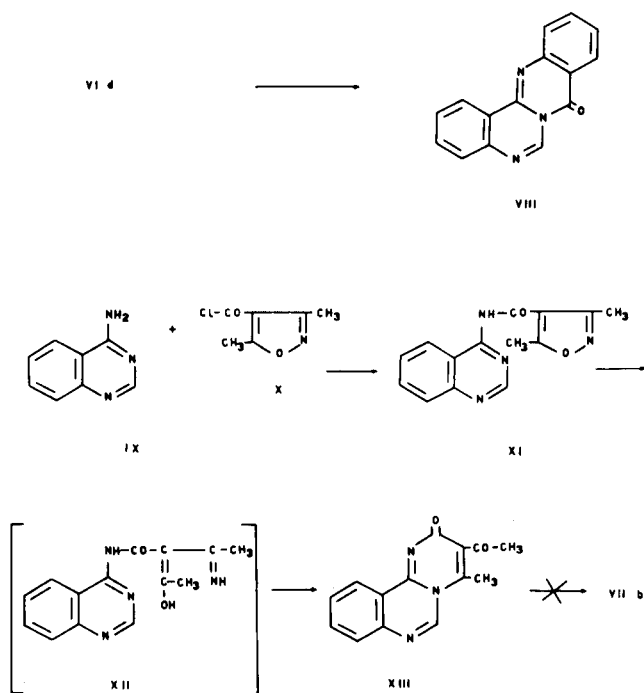
In a preliminary communication, we reported (1) the synthesis of 2 (or 4)phenylpyrimido[1,2-*c*]quinazolin-4 or 2-one (VIa or VIIa), *via* the reaction of 2-*o*-amino-phenyl-6-phenylpyrimidin-4(3*H*)one (Va) with formic acid. The compound Va was conveniently prepared by hydrogenolysis and further base-catalyzed cyclization of *o*-nitro-*N*-(3-phenyl-5-isoxazolyl)benzamide (IIIa) and its structure was confirmed by the fact that by reductive diazotization 2,6-diphenylpyrimidin-4(3*H*)one was obtained, which was identified by a mixed melting point and comparison of spectroscopic data with those of an authentic specimen (1). However, no structural elucidation either chemical or spectral for the compounds VIa or VIIa was presented (Scheme I). This report was a significant development in view of our interest in the synthesis of derivatives of this heterocycle of potential biological importance, bearing different functional groups or an alicyclic system fused

at positions 2 and 3 (Table II). The two approaches that we have employed to establish that compounds VI (VIIa, b, c, d) were, in fact, -4-ones, involved the effect of Eu (DPM)₃ shift reagent (2) on their pmr spectra (these results are summarized below) and the fact that VIa in decalin with Pd-C was dehydrogenated to VIII as shown with an authentic sample (3) (Scheme II). Furthermore, we had approached the problem of unequivocal synthesis of compound VIIb from a classical standpoint and had considered the conversion of amide XI into the acetyl derivative XIII (Scheme II), following the method described by one of us in a previous paper (4). Several attempts made to deacetylate XIII failed to give 4-methylpyrimido[1,2-*c*]quinazolin-2-one (VIIb).

Shift Reagent Proton Magnetic Resonance Spectra.

Confirmation of the structure of the pyrimido[1,2-*c*]-

Scheme II



quinazolinones as the -4-ones came from observing the deshielding effects produced by Eu (DPM)₃ shift reagent (2) on the normal spectrum of VIa. The preferential complexing of the europium derivatives paramagnetic shift reagent with the carbonyl oxygen of cyclic amides has been shown (5); thus the complexing of the Eu (DPM)₃ were the amide oxygen to be at C₂ would deshield predominantly the proton at C₃, while complexing with the carbonyl oxygen at C₄ would deshield predominantly the protons at C₃ and C₆. The pmr spectrum obtained with VIa is shown in Figure 1a; 6.88 δ (s, 1, H₃), 7.20-9.00, δ (m, 9, C₆H₄ and C₆H₅), 9.36 δ (s, 1, H₆). The addition of Eu (DPM)₃ in increments, produced the progressive downfield chemical shifts seen in Figure 1b, and c; the H-3 and H-6 proton chemical shifts are most affected to the extent of ca. 2.29 and 4.43 ppm respectively, and these are significantly larger than those induced on the remaining protons, ca. 0.3-0.4 ppm. Similar results were obtained by the use of the same shift reagent with VIb, c.

The original spectrum of VIb showed signals at 6.35 δ (s, 1, H₃) and 9.33 δ (s, 1, H₆). The addition of Eu (DPM)₃ in increments, produced downfield chemical shifts ca. 1.87 and 2.73 ppm respectively. In the case of VIc,

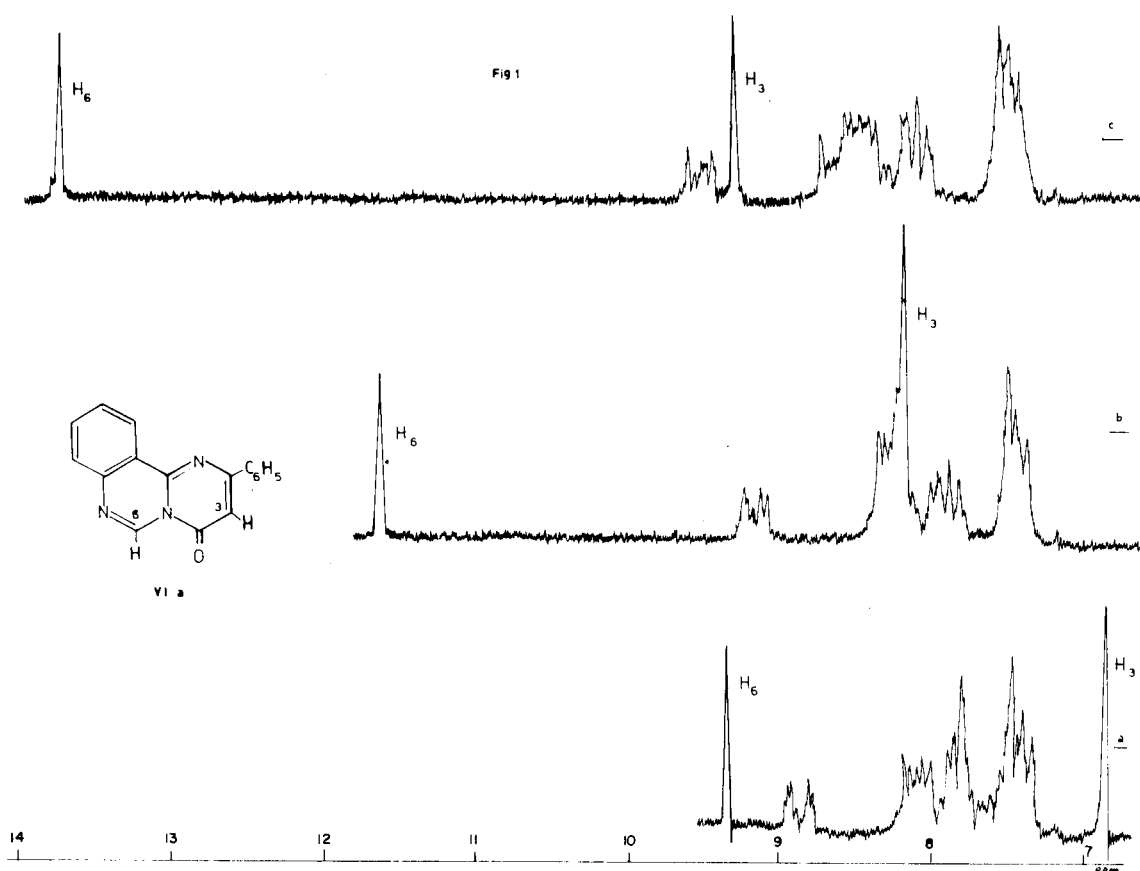


TABLE I

o-Nitro-*N*-(5-isoxazolyl)benzamides and 2-*o*-Aminophenylpyrimidin-4(3*H*)ones

	R	R'	M.p., °C	Formula	Analyses					
					Calcd. C	Calcd. H	Calcd. N	Calcd. C	Found H	Found N
IIIb	CH ₃	H	176-177	C ₁₁ H ₉ N ₃ O ₄ (a)	53.44	3.67	17.00	53.24	3.67	16.73
IIIc	C ₆ H ₅	CH ₃	204-207	C ₁₇ H ₁₃ N ₃ O ₄ (b)	63.15	4.05	13.00	63.39	4.21	12.86
III d	(CH ₂) ₄		176-178	C ₁₄ H ₁₃ N ₃ O ₄ (c)	58.53	4.56	14.63	58.37	4.72	14.72
Vb	CH ₃	H	218-220	C ₁₁ H ₁₁ N ₃ O (d)	65.67	5.51	20.88	65.71	5.32	21.00
Vc	C ₆ H ₅	CH ₃	255-257	C ₁₇ H ₁₅ N ₃ O (e)	73.63	5.45	15.15	73.45	5.55	15.03
Vd	(CH ₂) ₄		230-234	C ₁₄ H ₁₅ N ₃ O (f)	69.59	6.27	17.42	69.56	6.14	17.52

(a) Ir: 3220 (broad) (NH), 1660 cm⁻¹ (CO). (b) Ir: 3240 (NH), 1680 cm⁻¹ (CO). (c) Ir: 3240 (NH), 1680 cm⁻¹ (CO). (d) Ir: 3400, 3280, 3140 (NH, NH₂), 1670 cm⁻¹ (CO); nmr (DMSO-d₆): 2.22 δ (3H, s, CH₃), 6.10 δ (1H, s, pyrimidine CH), 6.40-7.80 (6H, m, C₆H₄ and NH₂), 11.00 δ (1H, broad, NH). (e) Ir: 3340, 3240, 3160 (NH, NH₂), 1670 cm⁻¹ (CO); nmr (DMSO-d₆): 2.00 δ (3H, s, CH₃), 6.40-7.80 δ (11H, m, C₆H₄, C₆H₅ and NH₂), 11.00 δ (1H, broad, NH). (f) Ir: 3460, 3280, 3160 (broad) (NH, NH₂), 1670 cm⁻¹ (CO); nmr (DMSO-d₆): 1.50-2.70 δ (8H, m, (CH₂)₄), 7.30-7.80 δ (6H, m, C₆H₄ and NH₂), 11.00 δ (1H, broad, NH).

TABLE II

Pyrimido[1,2-*c*]quinazolin-4-ones

	R	R'	M.p., °C	Formula	Analyses					
					Calcd. C	Calcd. H	Calcd. N	Calcd. C	Found H	Found N
VIb	CH ₃	H	188-190	C ₁₂ H ₉ N ₃ O (a)	68.23	4.30	19.90	68.46	4.31	19.78
VIc	C ₆ H ₅	CH ₃	220-222	C ₁₈ H ₁₃ N ₃ O (b)	75.24	4.56	14.63	75.51	4.85	14.34
VId	(CH ₂) ₄		184-186	C ₁₅ H ₁₃ N ₃ O (c)	71.69	5.21	16.72	71.87	5.24	16.70

(a) Uv λ max nm log ε 364 sh (4.27), 346 (4.42), 332 sh (4.32), 288 (4.57), 267 sh (4.51); ir: 1700 cm⁻¹ (CO); nmr: 2.45 (3H, s, CH₃), 6.35 δ (1H, s, CH), 7.60-8.70 δ (4H, m, C₆H₄), 9.33 δ (1H, s, quinazoline H). (b) Uv λ max nm log ε 378 sh (3.94), 356 (4.11), 346 sh (4.11), 292 sh (4.41), 280 (4.48); ir: 1700 cm⁻¹ (CO); nmr: 2.31 δ (3H, s, CH₃), 7.20-9.00 δ (9H, m, C₆H₄ and C₆H₅), 9.40 δ (1H, s, quinazoline H). (c) Uv λ max nm log ε 368 sh (3.72), 352 (3.95), 342 sh (3.89), 289 (4.13), 278 sh (4.09); ir: 1700 cm⁻¹ (CO); nmr: 1.58-3.00 δ (8H, m, (CH₂)₄), 7.50-9.00 δ (4H, m, C₆H₄), 9.40 δ (1H, s, quinazoline H).

the methyl group at C₃ and H₆, which in the normal spectrum gave signals at 2.31 δ and 9.40 δ, respectively were shifted by addition of Eu (DPM)₃ in increments to the extent of *ca.* 1.92 and 2.85 ppm.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer infracolor 137 spectrophotometer; uv spectra were determined in ethanol solution with a Beckmann DB recording spectrophotometer. The nmr spectra (deuteriochloroform) (unless otherwise specified) were

obtained with a Jeol C-60H spectrometer (TMS as internal reference).

General Procedure for *o*-Nitro-*N*-(5-isoxazolyl)benzamide Derivatives.

Equimolar amounts of IIb (6), IIc (7), or II d (8) (10 mmoles) and I (10 mmoles) in benzene (25 ml.) with ten drops of pyridine were refluxed for 20 minutes. The benzene was removed under vacuum and the residue was mixed with water (50 ml.). The precipitate was collected and recrystallized from methanol, yield 60-65%. The products are listed in Table I.

General Procedure for the 2-*o*-Aminophenylpyrimidin-4(3*H*)one Derivatives.

A mixture of 10 mmoles of IIIb or IIIc or IIId, 300 ml. of ethanol and ca. 2 g. of W₂-Raney-Nickel (9) was hydrogenated in a Parr apparatus at 45-50 psi for 8 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the reduced products which were not isolated but were refluxed in ethanol (50 ml.) with a solution of 2 g. of potassium hydroxide in water (5 ml.) for 15 minutes. After evaporation of ethanol, the addition of saturated ammonium chloride solution (200 ml.) gave a precipitate which was collected and recrystallized. In case of IIIb, the solution was extracted with ether (3 x 150 ml.). The organic layer evaporated gave a residue which was recrystallized. The products were recrystallized from ethanol to yield 50-58% of the desired products V, which are listed in Table I.

General Procedure for the Pyrimidoquinazolines.

A solution of 2 mmoles of Vb, c, d in 15 ml. of formic acid was refluxed for 3 hours. Evaporation of the solvent left the title compounds in yields of 65-70% after recrystallization from ethanol. The products are listed in Table II.

Quinazolino[4,3-*b*]quinazolin-8-one (VIII).

To a solution of 4 mmoles of VIId in decalin (40 ml.), 0.4 g. of Pd/C (10%) was added. After refluxing for 8 hours, the catalyst was filtered and the filtrate was cooled to a solid separate which melted at 195-197° (ethanol). The melting point was not depressed on admixture with an authentic specimen (3).

Anal. Calcd. for C₁₅H₉N₃O: C, 72.86; H, 3.67; N, 17.00. Found: C, 73.03; H, 3.71; N, 16.94.

N-(Quinazolin-4-yl)-3,5-dimethyl-4-isoxazolecarboxamide (XI).

A solution of 10 mmoles of 4-aminoquinazoline (IX) (10) in pyridine (50 ml.) was treated with 10 mmoles of 3,5-dimethylisoxazole-4-carboxylic acid chloride (X) (11). After stirring at room temperature for 12 hours, the precipitate which separated was filtered and recrystallized (yield 65-68%), m.p. 245-248° (ethanol); ir: 1640 cm⁻¹ (CO).

Anal. Calcd. for C₁₄H₁₂N₄O₂: C, 62.68; H, 4.51; N, 20.89. Found: C, 63.11; H, 4.51; N, 20.68.

3-Acetyl-4-methylpyrimido[1,2-*c*]quinazolin-2-one (XIII).

A mixture of 3 mmoles of XI, 300 ml. of ethanol and ca. 2 g. of W₂-Raney-Nickel (9) was hydrogenated in a Parr apparatus at 45-50 psi for 3 hours at room temperature. Removal of the catalyst and evaporation of ethanol left the title compound, yield 78-80% after recrystallization, m.p. 170-173° (ethanol); uv λ max nm log ε 236 (4.50), 292 (4.25), 365 (4.26); ir: 1670 and 1680 cm⁻¹ (2 x CO); nmr (DMSO-d₆): 2.52 δ (s, 3, CH₃), 2.60 δ (s, 3, CH₃), 8.00-9.00 δ (m, 4, C₆H₄), 9.40 δ (s, 1, quinazoline CH).

Anal. Calcd. for C₁₄H₁₁N₃O₂: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.55; H, 4.58; N, 16.35.

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