A CONVENIENT SYNTHESIS OF PYRIDAZINO[4,5-b]QUINOLINES AND PYRROLO[3,4-b]quinolines

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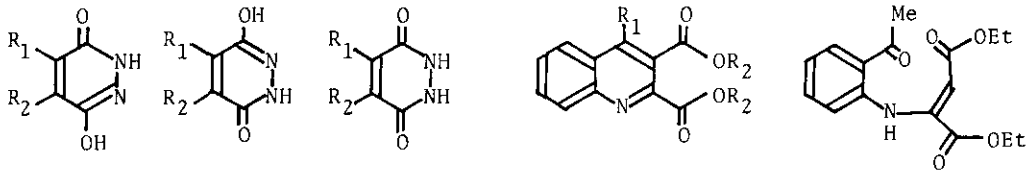
Abstract —— Pyridazino[4,5-b]quinolines were conveniently synthesized from the reaction of N-(1,2-bisethoxycarbonylvinyl)-o-aminoacetophenone with hydrazines, and 2,3-bishydrazinocarbonyl-4-methylquinolines were easily cyclized to pyrrolo-[3,4-b]quinolines.

Spectroscopic and crystallographic studies have been reported concerning the structure of maleic hydrazides[1,2,3,4,5] and other aromatic ring-condensed cyclic hydrazides[6,7,8] (pyridazines), which are clarified to be an oxo-hydroxy (I-a,b), but not dioxo (I-c), form in solution and solid state, as shown in Chart 1. Pyridazino[4,5-b]quinolines were prepared by the reaction of dimethyl acridinates (II) with hydrazine hydrate,[10,11] and its structure was proven to be the 1-oxo-4-hydroxy form by Godard.[11] Recently, we have also synthesized pyridazino[4,5-b]quinolines conveniently from the reaction of N-(1,2-bisethoxycarbonylvinyl)-o-aminoacetophenone (III)[12,13] with hydrazine hydrate and methylhydrazine. We now report a facile synthesis of the above condensed quinolines.

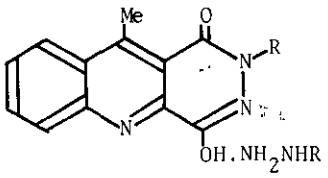
Refluxing of III (3.3 mmol) with hydrazine hydrate (6.6 mmol) in EtOH (15 ml) for 5 hr precipitated red needles, 4-hydroxy-10-methyl-1-oxo-1,2-dihydropyridazino[4,5-b]quinoline monohydrazinium salt (IV-a).[14] From its filtrate, yellow needles, 2,3-bishydrazinocarbonyl-4-methylquinoline (V-a),[15] were obtained. When V-a (0.88 mmol) was dissolved in H_2O (20 ml) and stirred for 30 min at room



(I-a) (I-b) (I-c) (II-a) R_1=Me, R_2=Me; (II-b) R_1=H, R_2=Me; (II-c) R_1=Me, R_2=Et (III)

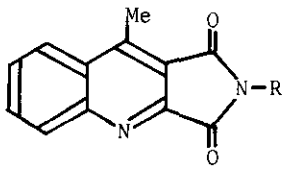
Chart 1

temperature, colorless needles, 2-amino-9-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-b]quinoline (VI-a)[16] (86%), were obtained. The reaction in the presence of 30-fold molar and equimolar amount of hydrazine hydrate against III mainly gave IV-a and V-a, respectively. A similar reaction of III (3.3 mmol) with methylhydrazine (33 mmol) also precipitated red needles, 4-hydroxy-2,10-dimethyl-1-oxo-1,2-dihydropyridazino[4,5-b]quinoline monomethylhydrazinium salt (IV-b).[14] From the filtrate, a yellow powder (V-b) (M^+=289) was obtained. In order to purify the yellow powder, it was submitted



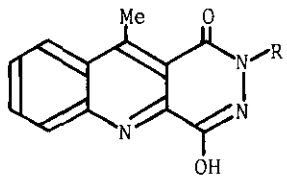
(IV-a) R=H
m.p. 245°(discolor)
310-315°(dec)

(IV-b) R=Me
m.p. 210°(discolor)
260-263°(dec)



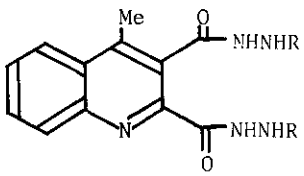
(VI-a) R=NH_2
m.p. 269-270°

(VI-b) R=NHMe
m.p. 240-241°



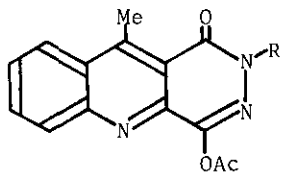
(VII-a) R=H
m.p. 326°(dec)

(VII-b) R=Me
m.p. 239-240°



(V-a) R=H
m.p. 323°

[(V-b) R=Me]



(VIII-a) R=H
m.p. 246-247°

(VIII-b) R=Me
m.p. 196-198°

Chart 2*

Table I.

Molar ratio (III) : $NH_2NH_2 \cdot H_2O$		Yield (%) (IV-a)	(V-a)	(VI-a)
1	1	trace	12	——
1	2	13	53	(47)**
1	30	88	——	——
(III) : NH_2NHMe		(IV-b)	(II-c)	(VI-b)
1	2	trace	94	——
1	10	30	——	27
1	30	94	——	——

* Satisfactory mass spectral and elemental analytical data were obtained for all new compounds.

** overall yield from (III)

to column chromatography to afford colorless needles, 9-methyl-2-methylamino-1,3-dioxo-1,3-dihydropyrrolo[3,4-b]quinoline (VI-b)[16] (M^+=234). This indicated that VI-b was formed from V-b during the column chromatography. The reaction in the presence of 30-fold and 2-fold molar amount of methylhydrazine against III predominantly resulted in the formation of IV-b and diethyl 4-methylacridinate (II-c),[12,13] respectively. In the molar ratio of 1:2, hydrazine hydrate produced IV-a and V-a, but not II-c. This may be due to the H_2O-content in the reaction media, which presumably varies the basicity or nucleophilicity of hydrazines. The above results are summarized in Table I, which suggests that III is converted to II-c, V, VII, and IV in sequence.

Treatment of the salts IV-a and IV-b with AcOH gave (VII-a) (93%) and (VII-b) (95%), respectively. The acetate (VIII-a) was obtained from both IV-a (56%) and VII-a (50%), and the acetate (VIII-b) was likewise obtained from both IV-b (80%) and VII-b (57%).

The compounds VI-a and VI-b were converted to IV-b (50%) and IV-a (30%) in the presence of excess of methylhydrazine and hydrazine hydrate, respectively. In this reaction, the intermediates were assumed to be the compounds V-a and V-b, from the results shown in Table I.

The compounds IV-a, VII-a, and VIII-a are assigned as the 1-oxo-4-hydroxy form, from the finding of Godard[11] described above. The compounds IV-b, VII-b, and VIII-b are also assumed to be the 1-oxo-4-hydroxy form, since the UV spectral patterns of these compounds are similar to those of IV-a, VII-a, and VIII-a, respectively. The signal for 10-methyl protons were observed at δ 3.40(VII-a), 3.38 (VII-b), 3.39(VIII-a), and 3.37(VIII-b), which were not varied significantly. Therefore, the compounds IV-b, VII-b, and VIII-b may be assigned as the 1-oxo-4-hydroxy form.

In conclusion, we found that pyridazino[4,5-b]quinolines were synthesized directly from the enamine adduct III, and 2,3-bishydrazinocarbonyl-4-methylquinolines V-a and V-b were easily converted to pyrrolo[3,4-b]quinolines.

Table II.

Compound	λ_{max} (EtOH) nm (logε)
(IV-a)	215.0(4.36) 248.0(4.72) 287.0(3.94)
(IV-b)	214.0(4.39) 249.0(4.71) 293.0(3.98)
(VII-a)	216.0(4.28) 248.5(4.71) 282.5(3.93)
(VII-b)	216.0(4.34) 249.0(4.69) 290.0(3.96)
(VIII-a)	228.5(4.37) 253.5(4.69) 296.0(3.87) 340.0(3.74) 357.5(3.66)
(VIII-b)	229.5(4.30) 254.0(4.68) 300.0(3.82) 340.0(3.77) 360.0(3.79)

References and Footnotes

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14. Further reflux of (IV-a) and (IV-b) in solutiond of hydrazine hydrate and methylhydrazine in EtOH gave analytically pure samples, respectively.
15. Compound (V-a): δ(DMSO-d_6) 9.22(2H, br.s, CONHNH$_2$), 8.47-7.50(4H, m, aromatic), 4.17(4H, br.s, CONHNH$_2$), 2.65(3H, s, 4-Me), ν(KBr) 3220(NH), 1655 and 1630(C=O).
16. δ(DMSO-d_6) 8.47-7.73(4H, m, aromatic), 5.15(2H, s, 2-NH$_2$), 3.03(3H, s, 10-Me), (VI-a); 8.43-7.63(4H, m, aromatic), 5.85(1H, q, J=6 Hz, 3-NHMe), 3.02(3H, s, 10-Me) 2.60(3H, d, J=6 Hz, 3-NHMe) (VI-b). ν(KBr) 1773 and 1700 (C=O) (VI-a), 1770 and 1715 (C=O) (VI-b). λ_{max} (EtOH) nm(logε) 215.0(4.36), 248.0(4.72), 287.0(3.94) (VI-a), 214.0(4.39), 249.0(4.71), 293.0(3.98) (VI-b).
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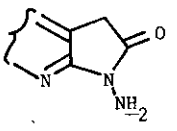

δ(DMSO-d_6) 5.25

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