

Cyclization of Ylidenemalononitriles. VI  
Studies on Nitrogen and Oxygen Heterocyclic Systems. (1)

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In an extension of studies on the acidic cyclization of ylidenemalononitrile adducts (I and II) from various  $\alpha$ -tetralones (2) and thiochromanones (3), we wish to report our results for the related nitrogen (III) and oxygen (IV) series.

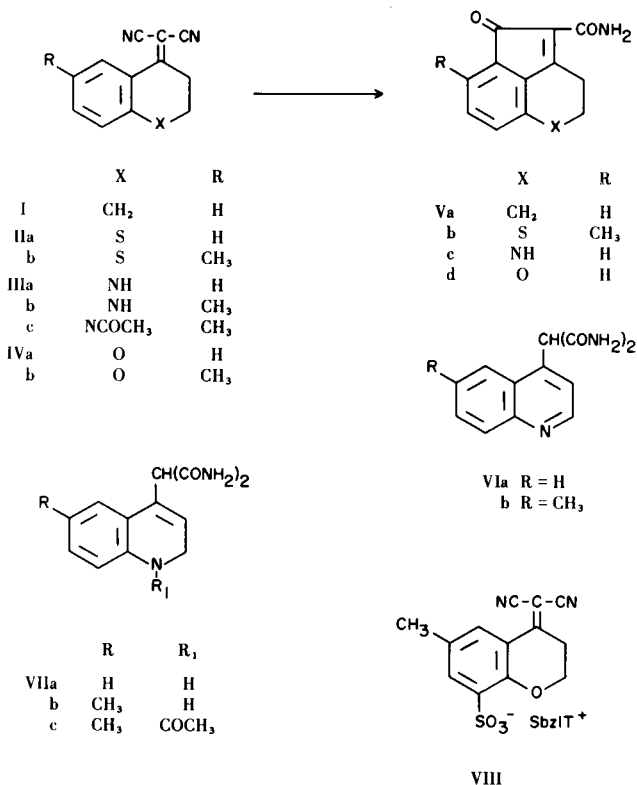
Richter (4) has reported that his attempts to cyclize the 4-( $\alpha,\alpha$ -dicyanomethylene)-1,2,3,4-tetrahydroquinoline (IIIa) did not give the desired ring closure (Vc), but instead he obtained a 4-quinolylmalonamide (VIa). It was suggested that this product most likely occurred by air oxidation of an intermediate 1,2-dihydro-derivative (VIIa), but this product was not isolated.

When we treated IIIa with sulfuric or polyphosphoric acid, water-soluble products were obtained, but not isolated or characterized. Although blocking the 6-position had prevented sulfonation and promoted cyclization in the sulfur heterocycle (3), treatment of the 6-methyl-4-( $\alpha,\alpha$ -dicyanomethylene)-1,2,3,4-tetrahydroquinoline (IIIb) with concentrated sulfuric acid at room temperature for one hour or at 60° for 2 hours gave no isolable products. When IIIb was heated with sulfuric acid at 130-140° for 30 minutes or with polyphosphoric acid at steam bath temperatures for 3 hours, an off-white product was obtained, whose elemental analysis, infrared, ultraviolet and nmr spectroscopy indicated that a relatively stable 1,2-dihydroquinolyl-4-malonamide (VIIb) had been isolated by this procedure.

Attempts to tosylate or benzoylate (Schotten-Baumann) the malononitrile adduct (IIIb), which would be expected to deactivate the benzene nucleus and facilitate ring closure, met with failure in our hands. Dark resinous products were usually obtained, which could not be suitably purified. However, when the adduct was refluxed with an acetic anhydride-sulfuric acid mixture, the *N*-acetylated product (IIIc) was obtained. Heating of the acetylated product with polyphosphoric acid gave the triamide (VIIc). The nmr spectra indicate that the double bond was in the 6-membered ring (endo) for the amides (VIIb and VIIc), whereas the double bond was exo to the 6-membered ring for the malononitrile adducts (see Table I). This difference in structure of the analogous systems III and VII may be steric, since the small cyano group does not inhibit coplanarity in the system, while the much

bulkier carboxamide group would provide steric strain, favoring VII. Isolation and characterization of the dihydroquinolyl-4-malonamides (VIIb and VIIc) supports the suggestion (4) that formation of the 4-quinolylmalonamide proceeded by oxidation of this intermediate (VIIa).

Treatment of chroman-4-ylidenemalononitrile (IVa) or 6-methylchroman-4-ylidenemalononitrile (IVb) with concentrated sulfuric or polyphosphoric acid gave only water soluble products. Salting, ether extraction or neutralization of the reaction mixture did not give isolable products. To establish that the products from sulfuric acid treatment were sulfonated, the *S*-benzylthiuronium 6-methylchroman-4-ylidenemalononitrile sulfonate (VIII) was isolated directly from the reaction mixture of an attempted sulfuric acid cyclization of IVb. Although attempts have not been made in every case to isolate the water soluble products, this example (VIII) confirms the view that



sulfonation may occur on attempted cyclization of compounds II, III, or IV in sulfuric acid.

There is ample evidence in the literature to indicate that oxygen atoms provide greater resonance interaction with aromatic nuclei than sulfur atoms (5,6). The bathochromic shift of the long wave length absorption band observed when the ultraviolet spectra of the analogous sulfur, nitrogen and oxygen heterocycles are compared (see Table II) is consistent with greater electronic interaction in the oxygen series, and this effect would account for the enhanced tendency to sulfonation in the chromanone and tetrahydroquinolone series.

TABLE I

NMR Spectra of Heterocyclic Ylidenemalononitriles ( $\tau$ ).

Compound	Aromatic Hydrogen (Ratio)	Methylene Hydrogen (Ratio)	Methyl Hydrogen (Ratio)
IIa (3)	1.9-2.15 (1) 2.5-3.0 (3)	6.5-7.1 (4)	---
IIb (3)	2.2 (1) 2.8 (2)	6.5-7.1 (4)	7.68 (3)
IIIa (4)	1.3-1.7 (1) 2.0-2.4 (3)	5.85-6.15 (2) 6.16-6.5 (2)	---
IIIb	1.6 (1) 2.3 (2)	5.85-6.1 (2) 6.2-6.5 (2)	7.45 (3)
IIIc	1.85 (1) 2.4 (2)	5.7-6.0 (2) 6.4-6.7 (2)	7.5 (6)
IVa	1.55-1.95 (1) 2.25-2.6 (1) 2.7-3.0 (2)	5.4-5.7 (2) 6.65-6.9 (2)	---
IVb	1.85 (1) 2.5-2.75 (1) 2.95-3.15 (1)	5.45-5.75 (2) 6.6-7.0 (2)	7.7 (3)

## EXPERIMENTAL (7)

## 1,2,3,4-Tetrahydroquinolones

Methyl  $\beta$ -anilino-propionate was prepared from aniline and methyl acrylate (134-137°/0.18 mm., Lit. (8) 156-160°/13-14 mm.). This was converted to *N*-tosyl- $\beta$ -anilino-propionic acid (m.p. 140-143°, Lit. (8) 144-146°) and cyclized in polyphosphoric acid (9) to give 1,2,3,4-tetrahydro-4-quinolone (m.p. 41-42.5°, Lit. (8,9) 43-44.5°, 38-40°).  $\beta$ -(*N*-Tosyl-*p*-toluidino)propionic acid was prepared by reacting *p*-toluidine and methyl acrylate followed by tosylation and hydrolysis of the ester (m.p. 115-118°, Lit. (9) 117-118°). 6-Methyl-1,2,3,4-tetrahydroquinolone was prepared by polyphosphoric acid cyclization of the  $\beta$ -(*N*-tosyl-*p*-toluidino)-propionic acid (m.p. 77-80°, Lit. (9) 81-83°).

## Chroman-4-ones.

$\beta$ -Phenoxypropionic acid was prepared by reacting  $\beta$ -propiolactone with an alkaline solution of phenol (10) (yield 14-24%) or

by the reactions of an alkaline solution of phenol with  $\beta$ -chloropropionic acid (11) (m.p. 97-98°, yield 21.5%). Under the same conditions,  $\beta$ -(*p*-methylphenoxy)propionic acid was prepared in low yields (13-20%; m.p. 144-146°, Lit. (10,11) 144-145°, 147-148°).

For the cyclization of the phenoxypropionic acids, the procedure of Loundon and Razdan (12) was utilized. This represents a slight modification of the Hurd and Hayao method (6). Chroman-4-one was obtained in a 75% yield (m.p. 35-38°, Lit. (12) 39°) and 6-methylchroman-4-one was obtained in an 84.2% yield (m.p. 29-31°, Lit. (13) 33-34°).

## Preparation of the Ylidenemalononitriles.

The method used was the same as that described in previous papers (2) following the procedure of Mowry (14). Some of the physical properties of the dinitriles are listed in Table III (15).

## 4-Dicarboxamidomethyl-6-methyl-1,2-dihydroquinoline (VIIb).

Two g. (0.0096 mole) of IIIb was slowly added to 40 ml. of concentrated sulfuric acid and this mixture was heated at 130-140° for 30 minutes. The dark reaction medium was poured onto ice-water. After addition of ammonium hydroxide, the basic solution was allowed to stand overnight. A crystalline product precipitated as yellowish-orange needles, which melted in the range 206-208°. A yield of 0.9 g. (38%) was obtained and the infrared spectrum indicated the presence of amide functional groups.

TABLE II

Ultraviolet Spectra of Heterocyclic Ylidenemalononitriles.

Compound	$\lambda$ max $m\mu$	$\epsilon$
IIa (3)	308	10,150
	270	10,100
	265	9,940
	250	10,000
IIb (3)	310	10,500
	273	10,830
	267	10,830
	243-247	13,000
IIIa (4)	314	9,750
	267-276 (shoulder)	4,750
	247	9,300
IIIb	318	12,000
	275-280 (shoulder)	5,220 - 4,930
	249	13,200
IIIc	363-377 (broad)	4,600
	309-312	9,750
	250-257 (shoulder)	7,950 - 7,400
	238	9,900
IVa	371	8,400
	305	12,700
	235-238 (shoulder)	5,600
	218	9,600
IVb	385	8,050
	305-310	13,800
	222	10,200

TABLE III

Preparation and Properties of Ylidenemalonitriles.

Compound	% Yield	M.p. °C	Molecular Formula	Carbon (Found)	Hydrogen (Found)	Nitrogen (Found)
IIIa (4)	60.3	162-163.5	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub>	73.83 (73.57)	4.65 (4.62)	21.52 (21.62)
IIIb	57.4	167-169	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub>	74.64 (74.15)	5.26 (5.62)	20.09 (20.26)
IIIc	66-77	128-131	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O	71.71 (71.55)	5.18 (5.14)	16.73 (16.31)
IVa	64.3	148-150	C <sub>12</sub> H <sub>8</sub> N <sub>2</sub> O	73.47 (73.29)	4.08 (4.47)	14.29 (14.10)
IVb	39.8	103-106	C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> O	74.29 (74.36)	4.76 (5.16)	13.33 (13.18)

Two g. of the malononitrile adduct was slowly added to 50 g. of polyphosphoric acid and the resulting red mixture was heated on a steam bath for 3 hours. By this time, the red mixture had become colorless. The polyphosphoric acid was decomposed with ice-water and the acidic medium was neutralized with ammonium hydroxide. A bright orange product, m.p. 206-209° (1.5 g., 64%) was recovered, which had an infrared spectrum identical to the product obtained from sulfuric acid; IR  $\lambda$  max (potassium bromide) 3350 (NH), 3180 (amido CO) and 1680 (amido CO)  $\text{cm}^{-1}$ ; U.V.  $\lambda$  max (95% ethanol) 234 ( $\epsilon = 24,800$ )  $\text{m}\mu$  (16). The crude product was not appreciably soluble in ethanol or acetone. After recrystallization from DMF-water, the bright yellow substance melted at 214-216°. A mixture melting point of the products from sulfuric and polyphosphoric acid was not depressed. An nmr spectrum supports the proposed structure for the diamide (VIIb). Peaks are shown at 2.6 (3H), 3.4 (1H), 5.0 (1H), 5.6-5.7 (2H) and 7.25-7.6 (3H) $\tau$  in the proper ratio.

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 63.67; H, 6.12; N, 17.14. Found: C, 63.43; H, 6.28; N, 17.16.

1-Acetyl-4-( $\alpha,\alpha$ -Dicyanomethylene)-6-methyl-1,2,3,4-tetrahydroquinoline (IIIc).

Five g. (0.024 mole) of IIIb was refluxed gently with 10 ml. of concentrated sulfuric acid and 50 ml. of acetic anhydride for 20 minutes. The mixture was cooled and poured onto crushed ice. The resulting product was recrystallized from 95% ethanol, to give 4.6 g. (77%) of a pale yellow substance (IIIc), melting in the range of 129.5-131°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O: C, 71.71; H, 5.18; N, 16.73. Found: C, 71.55; H, 5.14; N, 16.31.

1-Acetyl-4-dicarboxamidomethyl-6-methyl-1,2-dihydroquinoline (VIIc).

Three g. (0.012 mole) of IIIc was suspended in 30 g. of polyphosphoric acid and heated on a steam bath for 3 hours. The resulting dark reddish mixture was poured onto ice. After basification with ammonium hydroxide and standing overnight, a pale yellow product (VIIc) precipitated. The product was recrystallized from DMF-water to give 1.8 g. (52%) of a pale yellow material, melting at 248-250°; IR  $\lambda$  max (potassium bromide) 3400 (NH), 3200 (amido CO), and 1695-1620 (amido CO)  $\text{cm}^{-1}$ ;

U.V.  $\lambda$  max (95% ethanol) ( $\epsilon$ ) 295-310 (shoulder) (2,460), 272 (5,750) and 236 (31,200)  $\text{m}\mu$  (16); NMR 2.68 (3H), 3.38 (1H), 5.0 (1H), 5.25 (2H), 7.45 (3H) and 7.55 (3H) $\tau$ .

*Anal.* Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 62.72; H, 5.90; N, 14.63. Found: C, 62.45; H, 6.24; N, 14.47.

S-Benzylthiuronium 6-Methylchroman-4-ylidenemalononitrile Sulfonate (VIII).

Two g. (0.0095 mole) of IVb was suspended in 25 ml. concentrated sulfuric acid and heated on a steam bath for 2 hours. (Reaction at room temperature gave partial recovery of starting material). The reaction mixture was poured onto crushed ice to give water soluble products. The addition of excess sodium chloride did not effect precipitation of a sodium sulfonate. Attempts to extract a product from the acid or neutral mixture failed. When an excess (3 g.) of 2-benzyl-2-thiopseudourea hydrochloride was added to the sulfuric acid medium, previously saturated with sodium chloride, a yellow product was isolated, which was recrystallized from ethanol, after charcoal treatment, as flaky yellow crystals (2.8 g., 67%) melting at 234-235.5°; IR  $\lambda$  max (potassium bromide) 2220 (CN), 3300 (NH), 1200 and 1040 ( $\text{RSO}_3^-$ )  $\text{cm}^{-1}$ .

*Anal.* Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: C, 55.26; H, 4.39; N, 12.18; S, 14.04. Found: C, 55.44; H, 4.50; N, 12.00; S, 14.12.

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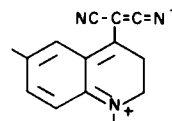
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