REVIEWS

Cyclization of Ylidenemalonodinitriles

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The utility of malonodinitrile in annelation reactions, via the intermediate ylidenemalonodinitriles, is reviewed. The method is shown to present a convenient pathway to the synthesis of a variety of cyclic compounds, including indenones, indanones, naphthalenes, lactones, and coumarins. Annelation may occur on heterocyclic rings which are susceptible to electrophilic substitution, and hetero atoms may be incorporated in more complex fused-ring systems. The cyclization is quite susceptible to differences in the character of the acidic cyclizing media, which allows selectivity in the kinds of products obtained.

Es wird eine Übersicht über die Verwendung von Malodinitril bei Annelierungsreaktionen mit Ylidenmalodinitrilen als Zwischenstufen gegeben. Die Methode ermöglicht auf einfache Weise die Synthese von Indenonen, Indanonen, Naphthalinderivaten, Lactonen, Cumarinen und weiteren Heterocyclen. Die Annelierung ist mit Heterocyclen möglich, die der elektrophilen Substitution zugänglich sind. Mehrfach kondensierte Heterocyclen sind damit erhältlich. Der Verlauf der Cyclisierung ist weitgehend von den sauren Bedingungen der Cyclisierung abhängig. Eine Wahl der Reaktionsprodukte wird dadurch ermöglicht.

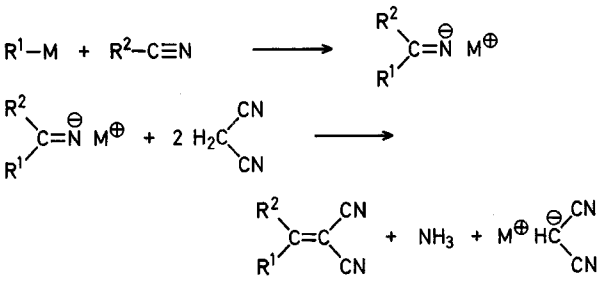
Much of the modern synthetic organic chemistry involves the use of "synthons", carbon fragments which are readily generated and introduced into molecules providing functional moieties available for further exploitation. One such synthon is malonodinitrile, a three-carbon fragment bearing functionality at each carbon atom. It has a distinct advantage over diethyl malonate in that its anion is more easily generated and less hindered, permitting condensations even with hindered carbonyl compounds, thus providing substituted ylidenemalonodinitriles which are useful intermediates in further reactions.

Ylidenemalonodinitriles are readily cyclized, providing an annelation technique which offers convenient synthetic pathways to substituted indenones, indanones, naphthalenes, lactones, and coumarins. These annelations are reviewed with a view to determine the scope and limitations of the reactions, as far as they have been tested.

1. Preparation of Ylidenemalonodinitriles

Synthesis of these reagents usually involves a typical Knoevenagel reaction between a carbonyl compound and malonodinitrile, catalyzed by base[1]. Yields in this condensation vary widely, and are poor with hindered ketones and diaryl ketones. Furthermore, the ketones required for specific syntheses are not likely to be commercially available, and must be synthesized, adding an isolation step which further reduces the yield of the desired product.

A convenient synthesis of ylidenemalonodinitriles has recently been described[2], which involves reaction of an organometallic reagent with a nitrile to produce a metal ketimate, followed by quenching with two equivalents of malonodinitrile. The ylidenemalonodinitriles are obtained in good yield, free of intermediate ketone, making this an especially useful synthesis where complex hindered ketones would have to be synthesized as intermediates.

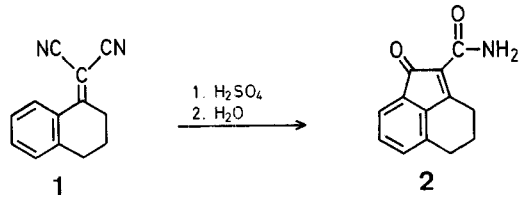


Preparation of 2-Cyano-3-isopropylcinnamonitrile[2]:
A dry ether solution of isobutyronitrile (1.75 g, 25 mmol) was added dropwise to an ether solution of phenyl Grignard reagent, prepared *in situ* from bromobenzene (3.92 g, 25 mmol). After stirring for 30 min, a solution of malonodinitrile (3.3 g, 50 mmol) in dry ether (50 ml) was added slowly with stirring. The resulting precipitate was dissolved by adding sufficient 10% hydrochloric acid. The ether layer was collected, washed with water and dried (magnesium sulfate). Evaporation of the ether left a yellow oily solid which was recrystallized once from ethanol as yellow crystals: yield: 3.6 g (75%); m.p. 56.0–57.5° (lit.[29] 60–62°).

Preparation of 2-Cyano-3-(2′-benzo[*b*]thienyl)-cinnamonitrile[2]:
A mixture of 2.5*M* *n*-butyllithium (24 ml, 60 mmol, hexane solution) in dry tetrahydrofuran (75 ml) was cooled to −78° in a 3-neck flask flushed with nitrogen, and benzo[*b*]thiophene (8.05 g, 60 mmol) dissolved in dry tetrahydrofuran (10 ml) was added all at once. The mixture was allowed to warm to room temperature with stirring, then cooled to −78° and benzonitrile (6.18 g, 60 mmol) in tetrahydrofuran (10 ml) added rapidly with stirring. After 30 minutes, malonodinitrile (7.92 g, 0.12 mol) in tetrahydrofuran (10 ml) was added, and the mixture stirred and allowed to warm to room temperature. After 1 h it was poured into ice and hydrochloric acid, ether added, and the tetrahydrofuran ether layer separated, washed with dilute sodium hydrogen carbonate and water, and dried (magnesium sulfate). Evaporation of the solvent left a rust-colored solid which was recrystallized twice from ethanol to give yellow crystals; yield: 15.5 g, (90%); m.p. 131.5–133°.

2. Cyclization to Form Five-membered Carbocyclic Rings

This reaction was first observed when α-tetrylidenemalonodinitrile, 1-dicyanomethylene-1,2,3,4-tetrahydronaphthalene (**1**) was dissolved in concentrated sulfuric acid and poured over ice. A nearly quantitative yield of bright yellow 2-aminocarbonyl-1-oxo-1,3,4,5-tetrahydroacenaphthylene (**2**) was obtained[3].

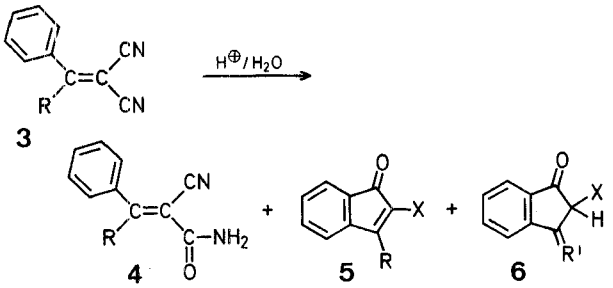


Preparation of 2-Aminocarbonyl-1-oxo-1,3,4,5-tetrahydroacenaphthylene (2)[3]:
A solution of α-tetrylidenemalonodinitrile (20 g, 0.1 mol) in 96% sulfuric acid (100 ml) was heated to 90° on a steam bath for 5 min, then cooled to 60° and poured over ice. The brown tarry oil solidified to an orange precipitate on standing. Two recrystallizations from 95% ethanol produced long orange needles of **2**; yield 17.8 g (84%); m.p. 203–205°.

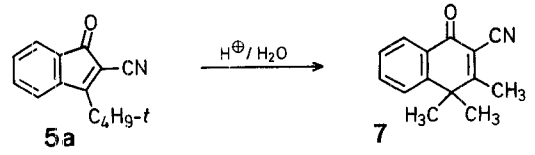
It was also possible to effect the cyclization with polyphosphoric acid, but yields were less, and some water-soluble products were formed (see later). This cyclization proved to be a quite general reaction, in which one of the nitrile groups, protonated, acted as an attacking electrophile to form a cyclic imine, later hydrolyzed to a ketone. The second nitrile may or may not be hydrated, depending on the degree of hindrance and the conditions of work-up from the aqueous acid.

2.1. Steric and Bulk Effects on Cyclization

In a series of β-substituted α-cyanocinnamonitriles (**3**) it was observed that the cyclization did not occur when R = H, only the cyanoamide **4** was formed[4]. When R = CH_3, the major product was **4**, but traces of indenone **5** were obtained. When R = C_2H_5 or *i*-C_3H_7, little of **4** was isolated, and the product consisted of about a 1:3 mixture of **5** and **6**. When R = *t*-C_4H_9 or C_6H_5, only the colored indenones **5** were isolated.



It is notable that when R = C_6H_5, the cyano function was retained in the initially isolated product (**5**, R = C_6H_5, X = CN) but X could be converted to aminocarbonyl by treatment with dilute aqueous acid. When R = *t*-C_4H_9 (i.e. **5a**), however, the nitrile isolated was too hindered, and has never been hydrated. This suggests that in the hydration of nitriles, the species attacking the protonated nitrile is larger than water. Perhaps the presence of the hydrogen sulfate ion is required. Attempts to hydrate **5a** (X = CN, R = *t*-C_4H_9) in concentrated acid resulted in an interesting ring enlargement reaction with methyl migration, forming **7** in good yield[5]. This facile sequence of neopentyl rearrangements should be useful in synthesizing functionalized tetrahydronaphthalenes bearing a quaternary carbon atom on the ring.



[1] G. Jones, *Org. React.* **15**, 204 (1967).
[2] E. Campaigne, D. E. Mais, E. M. Yokley, *Synth. Commun.* **4** 379 (1974).
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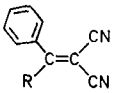
[4] E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, D. R Maulding, *J. Org. Chem.* **27**, 4428 (1962).
[5] E. Campaigne, D. R. Maulding, *J. Org. Chem.* **28**, 1391 (1963)

The increased ease of cyclization observed when R is larger than methyl in **3** suggests a buttressing effect of the β-substituent, forcing the protonated nitrile close to the aromatic ring. However, failure of **3** (R = H) to yield any cyclized product is surprising, until one realizes that **3** (R = H) is a highly conjugated planar system in which the aromatic ring is strongly deactivated toward electrophilic substitution by nitrile groups. It then becomes apparent that ring closure would be favored by a steric effect of R which would distort the structure of **3** by slightly rotating the aromatic ring, destroying coplanarity and inhibitory conjugation (i.e. reactivating the ring to electrophilic substitution) but not removing it completely from the reach of the protonated nitrile. The inference is borne out by the ultraviolet spectra of a series of **3** (Table 1). Quite clearly, the long wave length absorption (282–320 nm) attributed to the extended cinnamonitrile conjugated system of **3** decreases in intensity as more bulky substituents are incorporated at the β-position, while the short wave length adsorption (227–236 nm), attributed to the acrylonitrile absorption, increases in intensity. The two compounds **3**, R = H and R = *t*-C_4H_9, represent the extremes of these spectra.

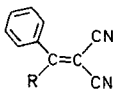
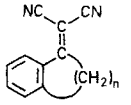
This series was further extended by Tindell[6] who prepared a series of **3** where R varied from *n*-propyl through *n*-hexyl (see Table 2). When these were cyclized in concentrated sulfuric acid, the *n*-propyl and *n*-butyl compounds (**3**, R = *n*-C_3H_7 or *n*-C_4H_9) behaved much like the ethyl derivative, giving a mixture of the two cyclized products **5** and **6**, with only a trace of the uncyclized hydrated product **4**. However, similar treatment of **3** (R = *n*-C_5H_{11} or *n*-C_6H_{13}) gave a mixture of all three products, in which 30 to 40% of the product was **4**. This observation is consistent with the enhanced intensity of the long wave length absorption of the pentyl and hexyl derivatives (Table 1) indicating that the aromatic ring is coplanar to the acrylonitrile system, hence deactivated. Why this should be so for pentyl and hexyl derivatives, but not for butyl, is not clear.

Table 2. New Ylidenemalonodinitriles, **3**[a]

Compound	b.p. or m.p.[c]	Yield (%)[b]	Molecular formulae[d]
			
3d R = *n*-C_3H_7	m.p. 55–56 °[c]	73	$C_{13}H_{12}N_2$ (196.2)
3e R = *n*-C_4H_9	106–108 °/0.7 torr	83	$C_{14}H_{14}N_2$ (210.2)
3k R = *i*-C_4H_9	m.p. 71–72 °[c]	95	$C_{14}H_{14}N_2$ (210.2)
3f R = *n*-C_5H_{11}	130–134 °/0.03 torr	97	$C_{15}H_{16}N_2$ (224.2)
3g R = *n*-C_6H_{13}	135–140 °/0.1 torr	89	$C_{16}H_{18}N_2$ (235.3)

[a] These compounds have not been previously reported.
[b] Using Knoevenagel conditions with ketone and malonodinitrile (cf. ref.[1]).
[c] Recrystallized from methanol.
[d] All compounds gave satisfactory microanalyses (C ± 0.3%, H ± 0.3%, N ± 0.3%).

Table 1. Ultraviolet Spectra of Some Ylidenemalonodinitriles[a, b]

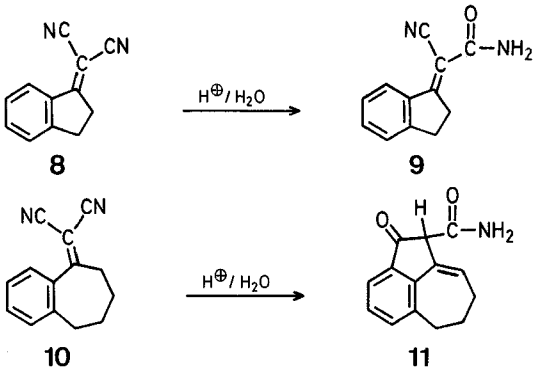
Compound	λ (nm)	ε	λ (nm)	ε
				
3a R = H	309	20,400	231	7,800
3b R = CH_3	292	12,800	232	7,600
3c R = C_2H_5	292	12,800	232	8,400
3d R = *n*-C_3H_7	292	11,560	233	7,540
3e R = *n*-C_4H_9	293	11,450	233	7,870
3f R = *n*-C_5H_{11}	292	14,250	232	8,870
3g R = *n*-C_6H_{13}	292	14,210	232	9,840
3h R = *i*-C_3H_7	283	5,400	232	10,900
3i R = *t*-C_4H_9	282	614	236	20,200
3j R = C_6H_5	320	1,900	227	14,400
				
8 n = 2	308	15,130	230	9,330
1 n = 3	313	13,200	231	5,750
10 n = 4	297	9,550	231	10,000

[a] Determined in 95% ethanol with a Cary Model 14 or Spectronic 505 spectrophotometer.
[b] The data are taken in part from ref.[4], in part from unpublished work by E. Campaigne and G. Tindell, and in part from ref.[7].

2.2. Influence of Ring Size and Hetero Atoms on Cyclization

Attempts to cyclize 1-indanylidenemalonodinitrile **(8)** yielded only the cyanoamide **9**[7] in which the aminocarbonyl group was shown by N.M.R.[8] to be exclusively *trans* to the aromatic ring (another example of hindrance to hydration of a *cis*-nitrile). On the other hand, 1-benzosuberylidenemalonodinitrile **(10)** was cyclized in excellent yield to give the tricyclic ketoamide **11**. Again, these results are

consistent with a high degree of conjugation of the aromatic ring with nitrile groups in **8**, which is less in **1** and **10**, as evidenced by the ultraviolet spectra (Table 1).

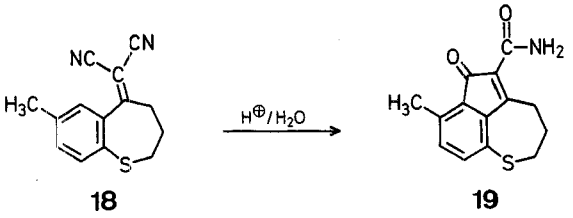


Preparation of 1-Aminocarbonyl-1,2,7,8-tetrahydro-6*H*-benz-[*c*,*d*]azulen-2-one (11)[7]:

Benzosuberylidenemalonodinitrile (**10**; 1.5 g, 6.6 mmol) was dissolved in polyphosphoric acid (30 g) and heated on a steam bath for 5 h. The hot, dark red, solution was poured over ice (120 g) and the pale yellow precipitate collected, washed with water, dried, and recrystallized from ethanol to give white prisms of **11**; yield: 1.0 g (60%); m.p. 188–189°.

These cyclizations have been extended to heterocyclic systems. It was found[9] that the reaction of 6-methylthiochroman-4-ylidenemalonodinitrile **(12a)** yielded the three disproportionation products **13, 14,** and **15.** From compound **12b** without the 6-methyl group, the sulfonated cyanoamide **16** was obtained[10] while the isomer of **12a** (namely **17**) yielded only intractable black crystals when subjected to similar cyclization conditions[10].

A mechanism proposed[9] for conversion of **12a** to **13, 14,** and **15** involving hydride transfer to a stable carbonium ion, has been recently supported[11] by formation of **19** from **18** and by the conversion of compound **13** to **14** and **15** under the same reaction conditions[10], indicating the intermediacy of **13.**



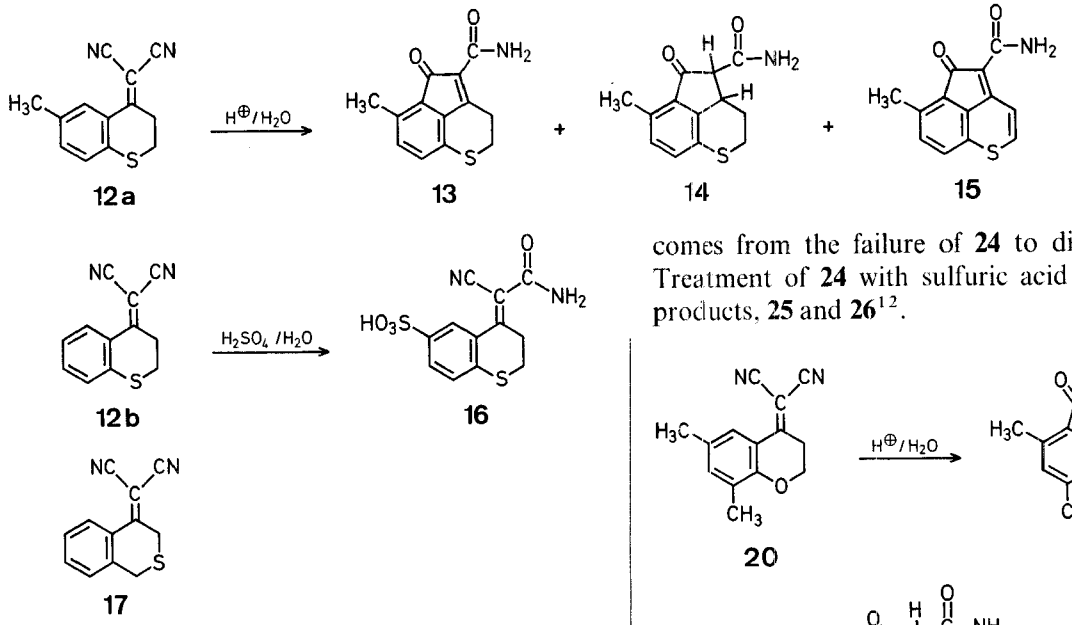
7-Methyl-6-oxo-2,3,4,4a-tetrahydro-indeno[7,1-*bc*]thiepin-5-carboxamide (19):

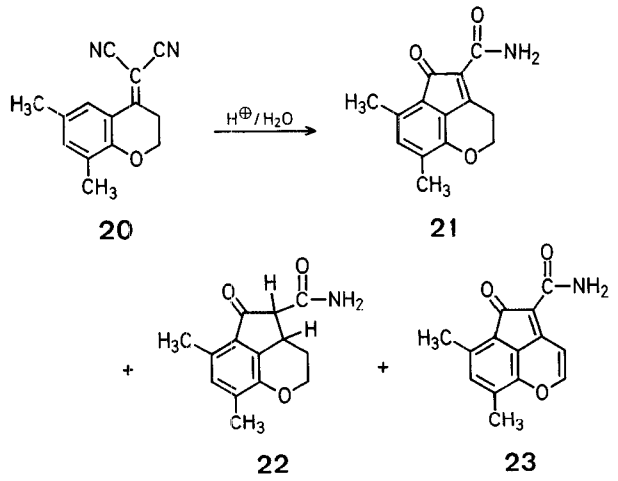
A concentrated sulfuric acid solution (60 ml) containing 7-methyl-2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-ylidene malonodinitrile[11] (**18**; 2.40 g, 0.01 mol) was stirred at room temperature until the blue color had persisted for 1 h (total reaction time 2 h). The solution was then warmed on a steam bath for 30 min and poured into a 1 l beaker of ice. After standing for several days, the brownish product was filtered and air dried. Thin layer chromatography on silica gel with ethyl acetate/benzene (1:2) showed one major product and two extremely minor constituents. Following column chromatography on silica gel employing ethyl acetate/benzene (1:9) **19**, m.p. 175°, was obtained in near quantitative yield (based on isolated material) as red prisms recrystallizable from absolute ethanol.

I.R. (KBr): ν_{max} = 1684, 1650 cm^{-1}

^{1}H-N.M.R. (DMSO-d_6): δ = 7.09 (q, 2H, aromatic), 3.72 (t, 2H, allylic or α to sulfur), 3.05 (t, 2H, allylic or α to sulfur), 2.33–2.72 ppm (methyl singlet at 2.50 ppm superimposed on a broad multiplet for hydrogens β to sulfur).

Disproportionation has also been observed[12,13] with the oxygen analog of **12a (20).** Inference that a hydride transfer from carbon-2 is operative here[12] comes from the failure of **24** to disproportionate. Treatment of **24** with sulfuric acid gave only two products, **25** and **26**[12].





[6] E. Campaigne, G. L. Tindell, Jr., unpublished results, 1968.

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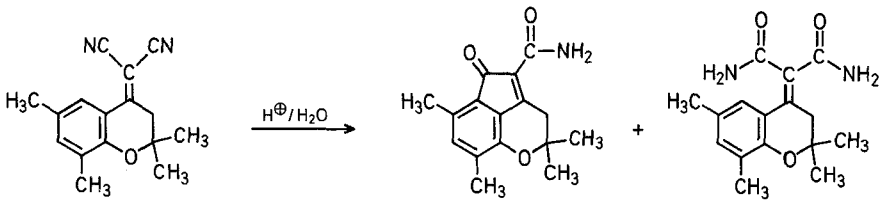
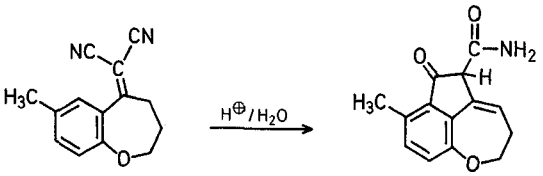


24 25 26

In both the sulfur and oxygen disproportionations the products are highly colored, and separable by fractional crystallizations, column chromatography, or preparative thin layer chromatography. In the case of the oxygen system **20** it was necessary to block[13] the positions *ortho* and *para* to the oxygen for successful ring closure[14], but in the sulfur system **(12)** blocking the *para*-position was sufficient[9,10].

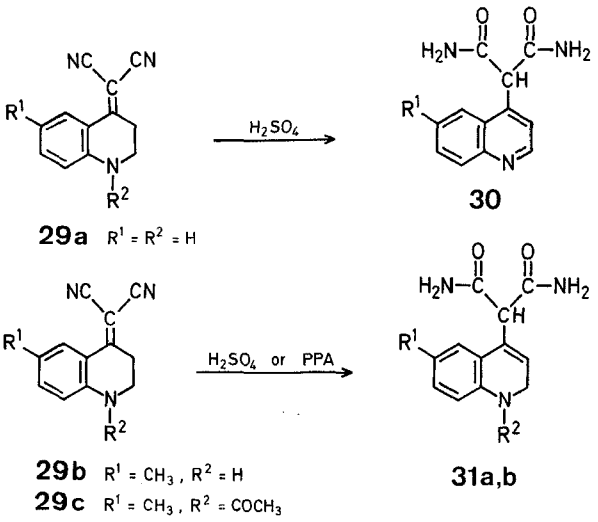
Treatment of **20** with polyphosphoric acid has recently been shown[15] to yield only compound **21** while **12a** in polyphosphoric acid produces the disproportionation series (i.e., **13, 14,** and **15**). The contrasting behaviors of **20** in polyphosphoric acid versus sulfuric acid and, in turn, between **12a** and **20** in polyphosphoric acid is difficult to rationalize. 7-Methyl-3,4-dihydro-1-benzoxepin-5(2*H*)-ylidenemalonodinitrile **(27)**, the oxygen analog of **18** has yielded **28**[16]. The same electronic-steric arguments advanced for the formation of **11** apply to **28** also. In this latter case, polyphosphoric acid on the 7-methylated ring was found to provide the only conditions for successful cyclization. In contrast to the chromanone case, the dinitrile **27** did not require a second methyl blocking group, suggesting that the distortion created by the seven-membered ring induced less oxygen-aromatic ring electronic interaction.



27 28

7-Methyl-6-oxo-2,3,5,6-tetrahydroindeno[7,1-*bc*]oxepin-5-carboxamide (28):
7-Methyl-3,4-dihydro-1-benzoxepin-5(2*H*)-ylidenemalonodinitrile[16] (**27**; 3 g, 13.4 mmol) was slowly added to mechanically stirred polyphosphoric acid (40 g) at 85°. The resulting solution became wine-red almost immediately and stirring was continued at 85° for 1 h. The resultant solution was poured in ice/water (1.8 l) and the insoluble material which resulted was filtered, washed with water, and air dried. Several recrystallizations from 95% ethanol gave **28** as white prisms; yield: 47%; m.p. 186–188°.
I.R. (KBr): ν_{max} = 1730 cm^{-1}, 1650 cm^{-1}
^{1}H-N.M.R. (DMSO-d_6): δ = 6.85–7.10 (br, 2H, aromatic), 6.09 (br, 1H, vinyl), 4.25 (t, J = 4 Hz, 2H, α to oxygen), 4.05 (broad s, 1H, methine), 2.12–2.43 ppm (5H, methyl singlet superimposed on multiplet of —CH_2— β to oxygen).
Mass spectrum: *m/e* (rel intensity) = 243 (72), 226 (62), 200 (79), 198 (47), 185 (50), 141 (47), 128 (48), 115 (94), 44 (100), and 18 (68).

Extension of the thiochroman and chroman studies to the quinoline ring system has been undertaken by two research groups[14,17]. When the ylidenemalonodinitrile of 4-oxo-1,2,3,4-tetrahydroquinoline **(29a)** was treated with concentrated sulfuric acid only the quinolylmalonamide **(30)** was obtained[17]. Similar attempts in our laboratories[14] led to only water soluble products. As a consequence, we blocked the 6-position **(29b)**, as was previously necessary with the sulfur and oxygen analogs, and realized the dihydro product **31a** with sulfuric or polyphosphoric acid. Likewise, use of the acetylated tetrahydroquinoline **(29c)**, which should deactivate the benzene ring toward substitution by the cyclizing medium, led to isolation of **31b.**



29a R^1 = R^2 = H **30**
29b R^1 = CH_3, R^2 = H **31a,b**
29c R^1 = CH_3, R^2 = $COCH_3$

[9] E. Campaigne, C. D. Blanton, Jr., *Tetrahedron Lett.* **1964**, 2489.
[10] E. Campaigne, H. R. Burton, C. D. Blanton, Jr., S. W. Schneller, *J. Heterocycl. Chem.* **8**, 65 (1971).
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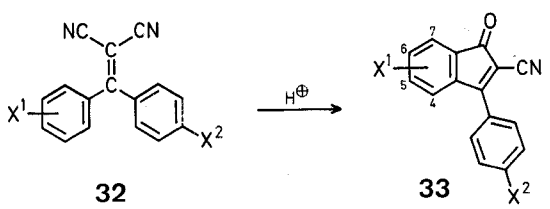
[18] R. F. Weddleton, *Ph. D. Thesis*, Indiana University, Bloomington, Indiana, 1965.

2.3. Electronic Effects of Substituents on the Aromatic Ring on Cyclization

Theoretically, substituents on the aromatic ring which are electron donors should enhance the cyclization if situated *ortho* or *para* to the site of electrophilic attack. However, investigation has shown that while this is generally true, sulfonation becomes a competing reaction, and other acid conditions, such as polyphosphoric acid, are required. The cyclization of several substituted α-tetralone derivatives[18] showed that the 7-methyl or 7-methoxy derivatives could be cyclized, but sulfonation of the cyclized product was a competing reaction. Better yields were observed in these cases in polyphosphoric acid. When the substituent was *meta* to ring-closure no cyclized products were identified from either sulfuric or polyphosphoric acid, and in the former, sulfonation and/or a retro-Knoevenagel hydrolysis occurred. The effect of ring substitution on the cyclization of β-methyl-α-cyanocinnamonitriles was examined[19], but only very poor yields of cyclized products were obtained, even with the *m*-methoxyacetophenylidenemalonodinitrile. The choice of substituted acetophenylidenemalonodinitriles to investigate the effect of substituents on the ring-closure was expedient, because of availability of starting ketones, but obviously not the ideal case since the parent acetophenone derivative gave such poor yields of cyclization products. The development of an alternate method of synthesizing ylidenemalonodinitriles from nitriles and organometallic reagents[2], provided a number of diphenylmethylidenemalonodinitriles **(32)**, with various substituents on one or both rings, in good yield. The cyclization of these derivatives has been studied[20]. As expected, the presence of an electron-releasing group, X^1, *ortho* or *para* to the site of ring-closure facilitated ring-closure to form **33** where X^1 appears at either the 5- or 7-position. This was true even when the substituent X^2 on the second ring was *p*-methyl or *p*-methoxy. These compounds could be cyclized in good yield in concentrated sulfuric acid or refluxing boron trifluoride-etherate complex, but polyphosphoric acid gave consistently poorer results (see Table 3).

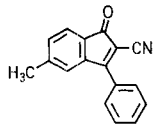
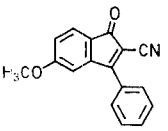
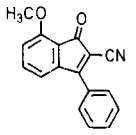
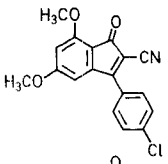
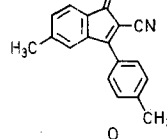
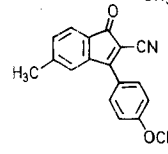
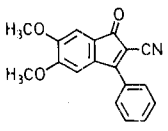


32 **33**

When X^1 was *m*-CH_3 in **32**, excellent yields of **33** (X^1 = 5-CH_3) were obtained in all three cases, where X^2 = H, CH_3, or CH_3O. When X^1 was *m*-H_3CO, however, a mixture of two products **33** (X^1 = 5-H_3CO or X^1 = 7-H_3CO, X^2 = H) was obtained in a ratio of about 2:1. These products were separable by column chromatography. It was also possible to cyclize **32** (X^1 = 3,5-di-H_3CO, X^2 = H) to **33** (X^1 = 5,7-di-H_3CO, X^2 = H) but in diminished yields.

Preparation of 2-Cyano-3-phenyl-5-methylindenone (33a):
A solution of 2-cyano-3-(*m*-tolyl)-cinnamonitrile (**32**, X^1 = *m*-CH_3, X^2 = H) (3.0 g, 12.3 mmol) in commercial boron trifluoride-etherate (50 ml; Eastman Kodak) was allowed to reflux for 1 h, then poured over ice with stirring. The mixture was extracted with chloroform, and the combined extracts dried (magnesium sulfate) and evaporated to dryness. Recrystallization from methanol gave yellow crystals of **33a**; yield: 2.4 g (80%); m.p. 187–188°; with characteristic I.R. absorptions for indenone carbonyl and cyano bonds.

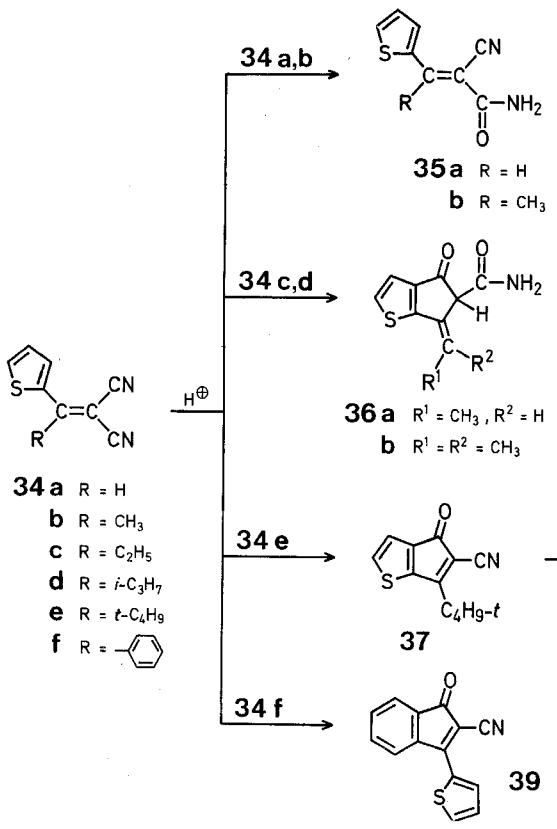
Table 3. Substituted 2-Cyano-3-arylindenones, **33**[a]

Compound		Yield (%)	m.p.[b]	Molecular formulae[c]
33a		86[d]	187–188°	$C_{17}H_{11}NO$ (242.3)
33b		38[e,f]	214–215°	$C_{17}H_{11}NO_2$ (258.3)
33c		22[e,f]	213–214°	$C_{17}H_{11}NO_2$ (258.3)
33d		48[f]	229–231°	$C_{18}H_{12}ClNO_3$ (325.8)
33e		60[d]	179–180°	$C_{18}H_{13}NO$ (259.3)
33f		76[d]	184–186°	$C_{18}H_{13}NO_2$ (275.3)
33g		80[d]	221–222°	$C_{18}H_{13}NO_3$ (291.3)

[a] These compounds have not been previously reported.
[b] All products were recrystallized twice from methanol.
[c] All compounds gave satisfactory microanalyses (C, H, N ±0.4%).
[d] Formed by cyclization of the appropriate **32** in sulfuric acid; see ref.[4] for details.
[e] Produced as a mixture from the cyclization of **32** (X^1 = *m*-H_3CO) and separated by column chromatography.
[f] See ref.[32] for details.

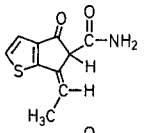
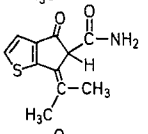
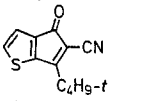
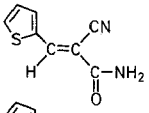
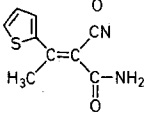
2.4. Cyclization to Aromatic Heterocyclic Systems

Application of this five-membered ring annelation technique to heterocyclic systems has been undertaken by Schneller and co-workers[12, 13], and preliminary results are available in the thiophene series[21]. In all cases it has been necessary to use polyphosphoric acid as the cyclizing medium since sulfuric acid appeared to open the thiophene ring (no sulfonated thiophenes could be detected). Compounds **34a** and **34b** yielded the uncyclized cyanoamides (**35a** and **35b**) in agreement with results in the phenyl series. Cyclization occurred exclusively to the cyclopentanothiophenes **36a** and **36b** with **34c** and **34d**, whereas **34e** yielded **37**. As in the carbocyclic series, **37** underwent ring expansion to the 5,6-system **38**. Finally, **34f**, which can cyclize in either of two directions, preferred to form the less strained 6,5-ring system (**39**) rather than the more strained 5,5-ring analogous to **37**. Steric strain accounts for the relatively low yields of **36a**, **36b**, and **37**, compared to yields in the conversion of **3** to **5** and **6**.



Treatment of Ylidenemalonodinitriles (34) with Polyphosphoric Acid: After polyphosphoric acid (200 g) had been warmed to the temperature required for reaction, **34**[21] (2.0 g) was added slowly under mechanical stirring. The resulting mixture was heated at 85–95° for 3 h (R = H), at 85° for 2 h for R = CH_3, at 50° for 2 h for R = C_2H_5, at 90° for 3 h for R = i-C_3H_7, or at 90° for 6 h for R = t-C_4H_9 and then cooled and poured over ice/water (500 ml) with vigorous stirring. After standing overnight the aqueous solution was filtered and the isolated product was air dried and purified to yield the products summarized in Table 4.

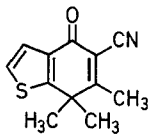
Table 4. Products from Acid Treatment of Thiopheneylidenemalonodinitriles

Compound	Yield (%)	m.p. (solvent)	Molecular formulae[a]
36a 	58[b]	210–211° (95% C_2H_5OH)	$C_9H_9NO_2S$ (195.2)
36b 	59[b]	221–223° (95% C_2H_5OH)	$C_{10}H_{11}NO_2S$ (209.3)
37 	33[c]	142–144° (C_2H_5OH/H_2O)	$C_{12}H_{11}NOS$ (217.3)
35a 	93[d, e]	166° (DMSO/H_2O)	$C_8H_6N_2OS$ (174.2)
35b 	86[f, g]	150–151° ($CHCl_3/C_6H_{14}$)	$C_9H_8N_2OS$ (192.2)

[a] All products gave satisfactory microanalyses (C ±0.37%, H ±0.29%).
[b] Colorless crystals.
[c] Red crystals.
[d] Light gray crystals.
[e] ^{1}H-N.M.R. (DMSO-d_6): δ = 4.50 (br, NH_2), 7.24 (t, H—C-4), 7.89 (m, H—C-3, H—C-5), 8.39 ppm (s, =CH—).
[f] Tan crystals.
[g] ^{1}H-N.M.R. (DMSO-d_6): δ = 2.58 (s, CH_3), 7.23 (t, H—C-4), 8.00 ppm (H—C-3, H—C-5), no signals for NH_2 could be detected.

2.5. Indenone-Indanone Equilibrium and Prototropy

It is apparent from the foregoing that cyclization of an ylidenemalonodinitrile may lead to a mixture of indenone and indanone (c.f. **5** and **6**), or to one or the other, depending on various factors which contribute to ring strain and to the energy of conjugation. Fortunately it is easy to follow the nature of the product, since the indenones are highly colored, while the indanones are colorless. In general, where a 5,6-fused ring system (c.f. **5** and **6**) is produced, a mixture of products favoring structure **6** in proportions of about 2:1 is found. These can usually be separated by differential solubility[4]. Compounds **5** were found to isomerize to **6** on an alumina column.

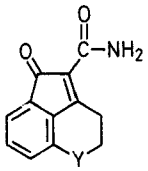


[19] D. R. Maulding, *Ph. D. Thesis*, Indiana University, Bloomington, Indiana, 1962.
[20] E. Campaigne, D. E. Mais, unpublished results, 1974.
[21] S. W. Schneller, D. R. Moore, *J. Org. Chem.* **40**, 1840 (1975).

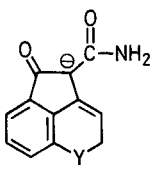
When the substituent R on **5** did not have an α-H atom, as when R = *t*-butyl or phenyl, then structures like **6** were impossible, and only **5** was obtained in good yield. It is interesting to note that in the more strained 5,5-fused system of **36**, only the white analogs of **6** could be obtained.

The indanones **6** were readily soluble in base forming colorless solutions which reprecipitated **6** on acidification. The yellow isomers **5** slowly went into solution on heating in base and lost color. Acidification then usually precipitated the indanone **6**, indicating stability of the anion of **6**, which is surrounded by three trigonal carbon atoms. Solution of the white isomers **6** in concentrated sulfuric acid regenerated the original equilibrium mixture (**5** and **6**) upon pouring over ice.

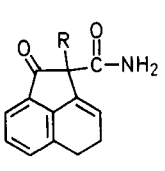
In some instances, however, the indanone structure is still too strained to be stable, and undergoes prototropy in solution to yield only the colored indenone. For example, in all of the 6,6,5-fused ring systems examined, (**40**, Y = CH_2, O, or S) only the indenones of structure **40** could be isolated in the pure state. In the case where Y = —CH_2—, it was found[22] that the bright yellow **40** formed a colorless solution in alcoholic methoxide, which on alkylation with an alkyl halide or allyl bromide produced the 2-alkylated products, **42** (see Table 5). Quenching the basic solution of **41** (Y = —CH_2—) in ice/acid mixture produced a white amorphous solid which turned orange upon melting and melted at the melting point of **40** (Y = —CH_2—). On warming this white solid in any possible crystallizing solvents, protic or aprotic, the solutions turned orange, and **40** (Y = —CH_2—) was crystallized.



40



41



42

Table 5. 2-Aminocarbonyl-2-alkyl-4,5-dihydroacenaphthen-1-ones[22]

Compound 42	R	Yield (%)[a]	m.p.[b]	Molecular formula
a	CH_3	89	200–202°	$C_{14}H_{13}NO_2$ (227.3)
b	C_2H_5	79	172.5–174°	$C_{15}H_{15}NO_2$ (241.3)
c	*i*-C_3H_7	76	185.5–187°	$C_{16}H_{17}NO_2$ (255.3)
d	H_2C=CH—CH_2—	63	105–106°	$C_{16}H_{15}NO_2$ (253.3)

[a] All compounds gave satisfactory microanalyses (C, H, N ±0.4%).

[b] Recrystallized from 95% ethanol.

Preparation of 2-Aminocarbonyl-2-methyl-4,5-dihydroacenaphthene-1-one[22] (42a):

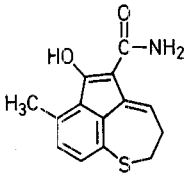
All compounds in Table 5 were prepared like the following example. A solution of **40**[3] (Y = CH_2; 4.0 g, 18.7 mmol) in acetone (100 ml) was treated with sodium hydride (33.3 mmol). The yellow solution became colorless as hydrogen was evolved. After stirring for 1 h, methyl iodide (10 ml) was added, the white precipitate was removed, water (250 ml) added, and the mixture heated on a steam bath to remove acetone and excess methyl iodide. On cooling, crude **42a** [yield: 4.4 g (100%); m.p. 181–188°] was obtained. Treating an alcohol solution of the product with Norite gave white crystals; yield: 4.0 g (89%); m.p. 200–202°.

I.R. (KBr): ν_{max} = 3448, 3185, 2940, 1698, 1669, 1590 cm^{-1}.

U.V. (ethanol): λ_{max} = 245 (ε = 21,900), 255–260 (shoulder, 17,100), 280 nm (shoulder, 6,820).

^{1}H-N.M.R. (DMSO-d_6): δ = 7.45 (m, 3H$_{arom}$), 7.1 (s, 2H, CONH$_2$), 6.01 (t, 1H, C=CH, J = 4Hz), 3.0–2.5 (m, 4H, CH_2) 1.48 ppm (s, 3H, CH_3).

In the case of the 5,6,7-fused ring systems derived from benzosuberylidenemalonodinitrile (**11**)[7] and its sulfur and oxygen heterocyclic analogs (**19** and **28**)[10,16] the strains induced in the ring systems are more subtle. For example, when **11** and **28** were precipitated from the cyclizing mixture, the crude product was yellow, but all purification attempts, by recrystallization or chromatography, produced only **11** or **28** in good yields. Alcoholic solution of **11** and **28** on warming turn yellow, but on cooling lose their color. So far, yellow indenone isomers of **11** and **28** have not been isolated in the solid state, but certainly traces are present in solution, and these may be trapped. Such experiments are under investigation. The sulfur analog, on the other hand, yields only the highly colored indenone **19**, and attempts to isomerize it have failed, but it may actually exist as an enol structure, **43**, which still maintains the 7-membered ring double bond in an even more conjugated system[11].



43

3. Cyclization of Saturated Malonodinitrile Derivatives

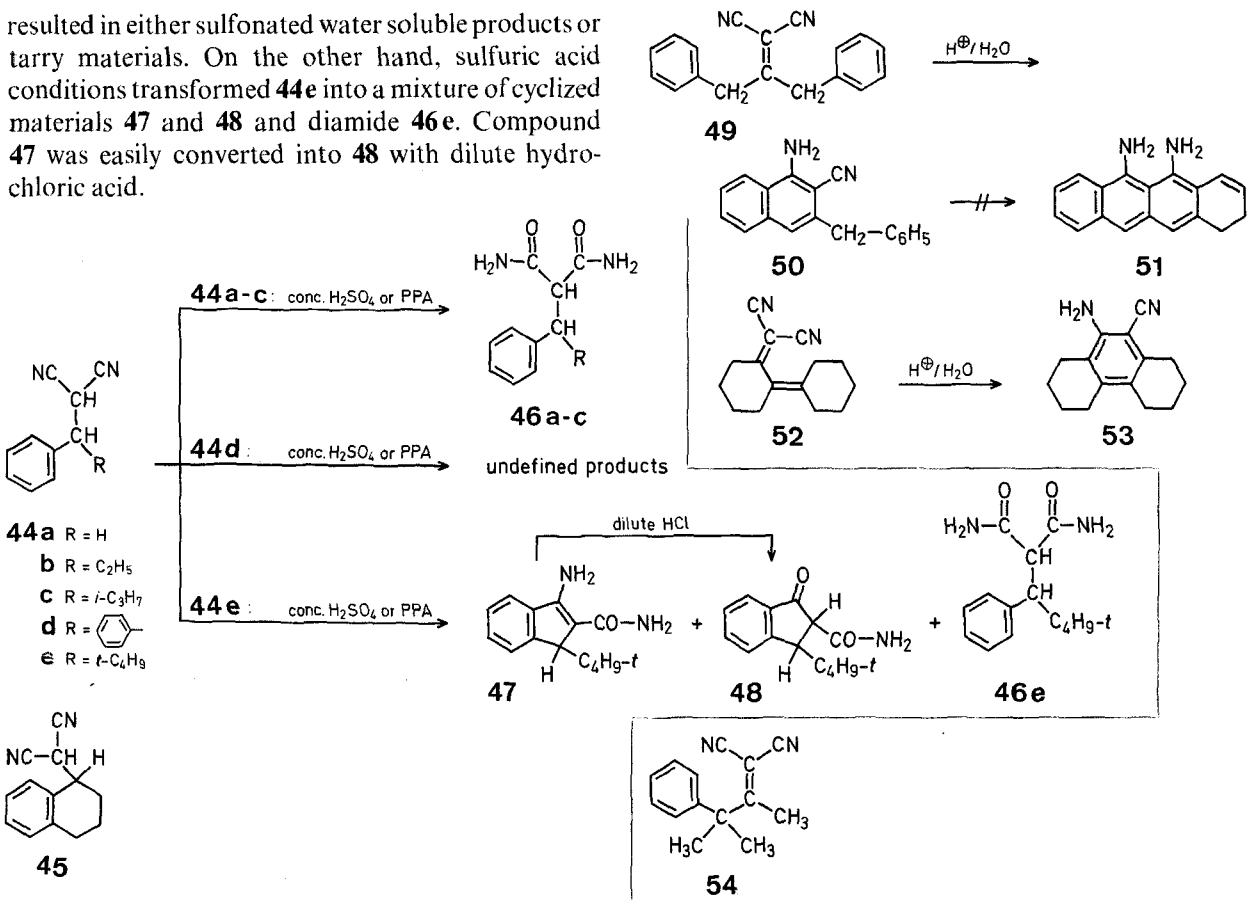
In order to better understand the role of substituents and distorted conjugation effects in the cyclization of ylidenemalonodinitriles, the saturated analogs of many of the systems already discussed (**44** and **45**)[23] have been examined.

Treatment of **44a–c** with concentrated sulfuric acid or polyphosphoric acid gave only the uncyclized diamides **46**. Similar treatment of **44d** and **45**

[22] D. Templer, *Ph. D. Thesis*, Indiana University, Bloomington, Indiana, 1966.

[23] E. Campaigne, W. L. Roelofs, *J. Org. Chem.* **30**, 396 (1965).

resulted in either sulfonated water soluble products or tarry materials. On the other hand, sulfuric acid conditions transformed **44e** into a mixture of cyclized materials **47** and **48** and diamide **46e**. Compound **47** was easily converted into **48** with dilute hydrochloric acid.



These results clearly indicate that ring closure occurs much less readily in the reduced series of ylidenemalonodinitriles. Only when a sufficiently bulky R group (t-C_4H_9) is present to force a nitrile group nearer the aromatic nucleus than in the other cases did the desired reaction occur. In the remaining cases loss of the sp^2 carbons (although removing the aromatic ring deactivating effect of the ylidene moiety) reduced rigidity and rendered the nitrile groups more susceptible to hydration than cyclization.

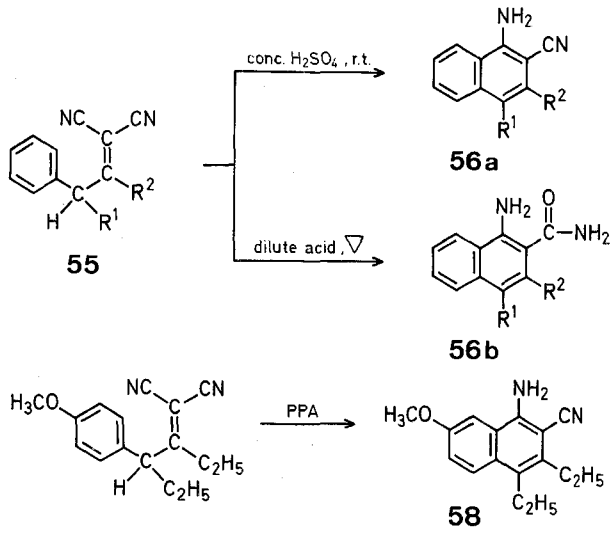
4. Cyclization to Form Six-membered Carbocyclic Rings

Prior to 1964 only three cyclizations of ylidenemalonodinitriles to form six-membered rings had been reported. These involved the cyclization of 1,3-diphenylisopropylidenemalonodinitrile **49**[24], the ring closure of 2-(cyclohexylidene)-cyclohexylidenemalonodinitrile **52**[25] and the cyclization of 3-methyl-3-phenyl-2-butylidenemalonodinitrile **54**, as an unequivocal synthesis of the ring-expanded product (**7**) from acid treatment of 2-cyano-3-t-butyl-1-indenone (**5a**)[5]. We have reexamined the cyclization of **49**, and in sulfuric acid it is readily converted to the α-naphthylamine **50**. We were, however, unable to effect the conversion of **50** to 11,12-diaminonaphthacene, **51**, even under the super acid conditions described by Dufraisse and Etienne[24].

[24] C. Dufraisse, A. Etienne, *Compt. Rend.* **239**, 1744 (1954); **240**, 265 (1955).

The cyclization of nitriles to form 6-membered cyclic ketones and aromatic amines is a well-known reaction[26], and the use of the conveniently available ylidenemalonodinitriles to produce variously substituted 2-cyano or 2-aminocarbonyl-1-naphthylamines was explored[27]. It was found that, in general cyclization of compounds of structure **55**, where R^1 or R^2 (or both) were methyl groups, gave excellent yields of the corresponding α-naphthylamines, **56a**, in concentrated sulfuric acid at room temperature. Heating in more dilute acid for longer periods hydrated the nitrile on **56**, to produce the aminoamides **56** (Z = —CO—NH_2). This was true even when R^1 and R^2 were part of a ring, as when **55** was 2-phenyl-cyclohexylidenemalonodinitrile (i.e., $R^1 + R^2 = -(CH_2)_4-$), which cyclized quite well in polyphosphoric acid to produce **57** (Z = —CO—NH_2) from the aqueous work up. The presence of a methoxy group *meta* to the ring-closure site on the aromatic ring led to tar formation in sulfuric acid (probably intermolecular acylation) but a low yield of **58** was obtained when 2-cyano-3-ethyl-4-(*p*-methoxyphenyl) 2-hexenonitrile was treated with polyphosphoric acid.

The presence or absence of a double bond in the side-chain, important in cases where 5-membered rings were formed, was of course not significant to forming 6-membered rings, since 2-carboxamido-3-methyl-1-oxotetrahydronaphthalene was readily formed in sulfuric acid from 2-cyano-3-methyl-4-phenylbutyronitrile[27].



Preparation of 9-Amino-10-cyano-1,2,3,4-tetrahydrophenanthrene (57, Z = CN)[27]:

A solution of 2-phenylcyclohexylidenemalonodinitrile (2.0 g, 10.7 mmol) in 96% sulfuric acid (20 ml) was allowed to stand in a stoppered flask for 6 h at room temp.; then poured over ice. The precipitate was filtered, and recrystallized once from methanol to give **57** (Z = CN) as white crystals; yield: 1.6 g (80%); m.p. 165–166°.

Preparation of 9-Amino-10-aminocarbonyl-1,2,3,4-tetrahydrophenanthrene (57, Z = $CONH_2$):

A solution of 2-phenylcyclohexylidenemalonodinitrile (2.0 g, 10.7 mmol) in polyphosphoric acid (80 g) was heated at 90° for 4 h, then poured into ice water (500 ml) and let stand overnight. The white solid was collected and recrystallized from methanol to give colorless crystals of **57** (Z = CO—NH_2); yield: 1.3 g (62%); m.p. 266–268°. Neutralization of the mother liquor with ammonium hydroxide produced a small second crop of the amide.

5. Formation of Lactones

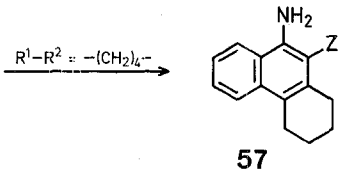
5.1. Synthesis of γ-Butyrolactones

It has been shown[28,29] that the acid used in the cyclization of ylidenemalonodinitriles has a pronounced effect on the nature of the isolated product. Those ylidenemalonodinitriles having a tertiary γ-hydrogen form lactones as the principal product in polyphosphoric acid but indenone-indanone mixtures in sulfuric acid. For example, it was shown[4] that **59** (R = C_6H_5) gave yields of the indenone-indanone mixture **60** in the order of 75–80% in concentrated sulfuric acid, but only about 10 to 15% in polyphosphoric acid. Work-up of the aqueous phosphoric acid solution after quenching produced the 2-aminocarbonyl-3-phenyl-4-methyl-γ-valerolactone **61** (R = C_6H_5) in yields up to 85%[29].

[25] H. Jaeger, *Chem. Ber.* **95**, 242 (1962).
[26] C. K. Bradsher, D. J. Beavers, E. D. Little, *J. Am. Chem. Soc.* **76**, 948 (1954); **78**, 2153 (1956).
[27] E. Campaigne, D. R. Maulding, W. L. Roelofs, *J. Org. Chem.* **30**, 1543 (1964).
[28] E. Campaigne, R. L. Ellis, *J. Chem. Soc. Chem. Commun.* **1966**, 141.
[29] E. Campaigne, R. L. Ellis, *J. Org. Chem.* **32**, 2372 (1967).

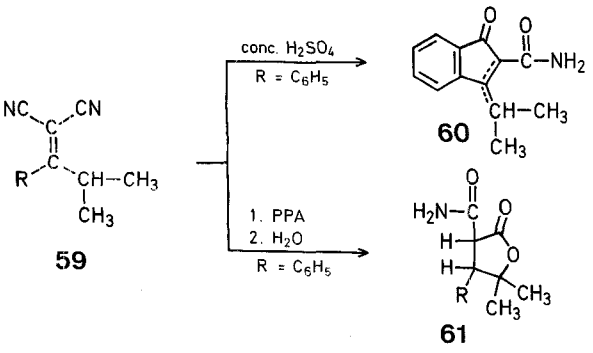
Preparation of 2-Aminocarbonyl-3-(4-chlorophenyl)-4-methyl-γ-valerolactone (61, R = 4-ClC_6H_4)[30]:

A mixture of 2-cyano-3-isopropyl-*p*-chlorocinnamonitrile (50 g, 0.216 mol) and polyphosphoric acid (500 g) was heated on a steam bath with stirring for 6 h, then poured into water (3 l), stirred for 2 h, and the solid collected, dissolved in ethyl acetate and

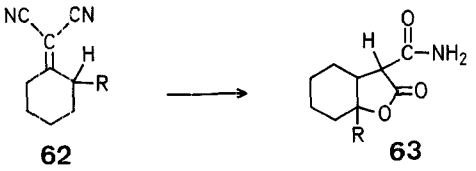


dried (magnesium sulfate). The ethyl acetate solution was then evaporated to about one-third of its initial volume, and hexane added until crystallization was complete. Recrystallization from ethyl acetate/hexane gave white crystals of **61** (R = 4-ClC_6H_4); yield: 49 g (85%); m.p. 178–179°.

I.R. (KBr): $\nu_{max} = 1695, 1770\ cm^{-1}$.

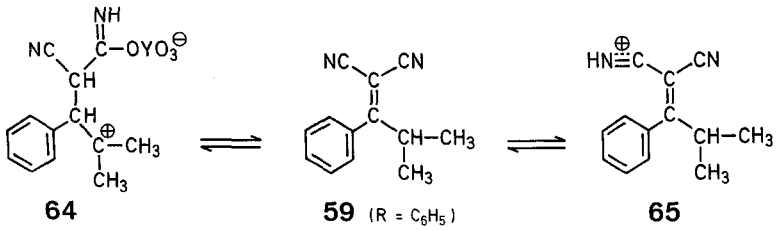


A number of examples of **59** were examined, where R = C_6H_5, *i*-C_3H_7, CH_3, or H and in polyphosphoric acid, all of these compounds produced the corresponding aminocarbonyl-lactones **61** in good yield. It was necessary to have a γ-tertiary hydrogen for the reaction to occur in all of the open-chain systems investigated, but in the cyclohexylidenmalonodinitrile systems **62** (R = H or CH_3), while lactone formation was facilitated by the tertiary hydrogen at the γ-position (**62**, R = CH_3) and ring-closure occurred only at that position to give **63** (R = CH_3), still cyclization of the unsubstituted cyclohexylidenemalonodinitrile **62** (R = H) occurred in satisfactory yield to give **63** (R = H).



Conversion of unsaturated acids to lactones, when the double bond is able to migrate (in some cases with skeletal rearrangement) is well documented[30]. The formation of lactones directly from unsaturated nitriles is less common and those reported have not involved double bond migration[31]. While a plausible mechanism for conversions of unsaturated acids, esters or amides to lactones is easily visualized[30] it cannot be applied directly to the unsaturated nitrile

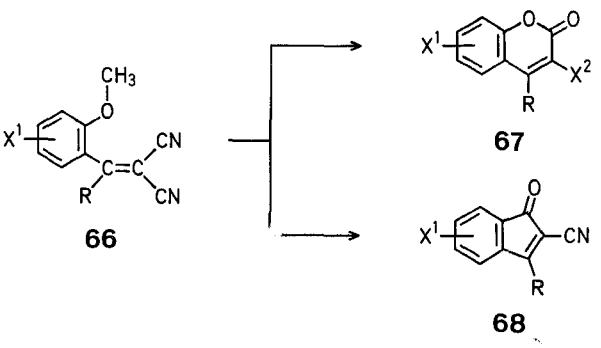
system, which requires the incorporation of an extra atom of oxygen. The different results obtained when **59** ($R=C_6H_5$) is treated with sulfuric acid compared with polyphosphoric acid may be accounted for by a difference in ease of displacement of oxidized sulfur in sulfate. Thus **59** ($R=C_6H_5$) in sulfuric or polyphosphoric acid solution yields an equilibrium mixture of **64** (Y = S or P) and protonated **59** (**65**). Conversion of **64** (Y = P) to lactone **61** by displacement of oxidized phosphorus is more rapid than cyclization of **65** to **60**, while the corresponding reaction of **64** (Y = S) is much slower.



64 **59** ($R = C_6H_5$) **65**

5.2. Synthesis of Coumarins

Another example of different reaction pathways in cyclization with different acid catalysts has been observed in the cyclization of *o*-methoxybenzylidenemalonodinitriles[32]. In concentrated sulfuric acid, the *o*-methoxy derivatives **66** (R is aromatic) were converted in good yield to the corresponding coumarins **67**, where $X^2=CN$. In more dilute acid these were converted to **67**, $X^2=CO—NH_2$, but when R = H in **66**, only **67** ($R=H$, $X^2=CO—NH_2$) was obtained directly from concentrated acid. A number of such cyclizations could be affected, and no indenones, **68**, were observed under these conditions, even when a second methoxy group activated the ring *para* to the site of possible acylation. For example **66** ($R=C_6H_5$, $X^1=3\text{-}H_3CO$) in sulfuric acid gave **67** ($R=C_6H_5$, $X^1=6\text{-}H_3CO$, $X^2=CN$) in 83% yield.



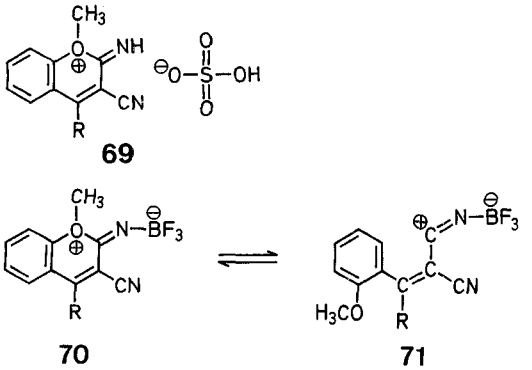
66 **67** **68**

Preparation of 3-Cyano-4-(4-chlorophenyl)-6-methoxycoumarin (67, $X^2=CN$, $R=C_6H_4Cl\text{-}4$, $X^1=CH_3O$)[33]:

A solution of 2-cyano-3-(4-chlorophenyl)-2′,5′-dimethoxycinnamonitrile (**66**, $R=C_6H_4Cl\text{-}4$, $X^1=5'\text{-}H_3CO$)[33] (32.4 g, 0.1 mol) in 96% sulfuric acid (100 ml) was warmed on a steam bath for about 20 min with stirring, then poured over ice. When the ice had melted, the crude solid was collected, washed, dried, and recrystallized from methanol to give white crystals of **67**; yield: 25.8 g, (83%); m.p. 242–244°.

In view of the facile cyclization of diphenylmethylidenemalonodinitrile bearing an electron releasing group *ortho* or *para* to the site of ring closure to form the indenones (e.g., **32**→**33**)[20], it is remarkable that no indenones were isolated from the sulfuric acid treatment of **66**, even when the position of electrophilic attack was activated. The indenones **68** could be obtained in good yield (69–70%) however, by refluxing the appropriate **66** in boron trifluoride etherate. In these cases traces of the coumarins could also be separated, but the two reagents appear to be quite selective. Several indenones **68**, where $R=C_6H_5$, and $X^1=H$, 5-H_3CO, 6-H_3CO, or 7-H_3CO were obtained.

The different results obtained when different acid catalysts were used in this reaction must be caused by a deficiency of nucleophile present in the boron trifluoride cyclization. The reaction undoubtedly involved attack on the ether oxygen by the electrophilic nitrile-acid complex to produce the ion **69** in sulfuric acid or **70** in boron trifluoride-etherate. In the case of **69**, however, there is hydrogen-sulfate ion present, which can act as a nucleophile to displace the methyl group from the oxonium ion as methyl hydrogen sulfate, and form the lactone on final hydrolysis. The ionic intermediate **70** has no nucleophile available for further reaction, and must be in equilibrium with the nitrile-boron trifluoride complex **71** which can react by electrophilic acylation of the aromatic ring leading to the indenones **68**. The presence of traces of coumarins found in these cases must be due to moisture in the reagents, providing traces of a nucleophile to react with **70**.



69 **70** **71**

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6. Conclusion

In the studies described above, we have shown that the ylidenemalonodinitriles provide a useful system for building additional rings, both carboxylic and heterocyclic, and that annelation may occur on carboxylic and heterocyclic systems. The systems are subject to electronic effects and steric strains, some of which are quite subtle. These cyclization systems are also quite susceptible to differences in the character of the acidic cyclizing media, which allows for selectivity in the kinds of reaction products obtained. The scope and limitations of these various cyclization are still under investigation in our laboratories, but sufficient information is now available and surveyed here to suggest some practical synthetic utility for this reaction.

We wish to express our sincere appreciation to our co-workers, who are named in the references, for their experimental enthusiasm and intellectual contributions to this work. We gratefully acknowledge the support of the Petroleum Research Fund, administered by the American Chemical Society, for the work of S. W. Schneller and his students at the University of South Florida, and the support of the National Institutes of Health, U. S. Public Health Service and the Bristol Laboratorires of Syracuse, N. Y., for the work of E. Campaigne and his students at Indiana University.

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