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Studies on Heterocyclic Enaminonitriles. VII.[1] Reactions of 2-Amino-3-cyano-4,5-dihydrothiophenes with Acetylenic Esters

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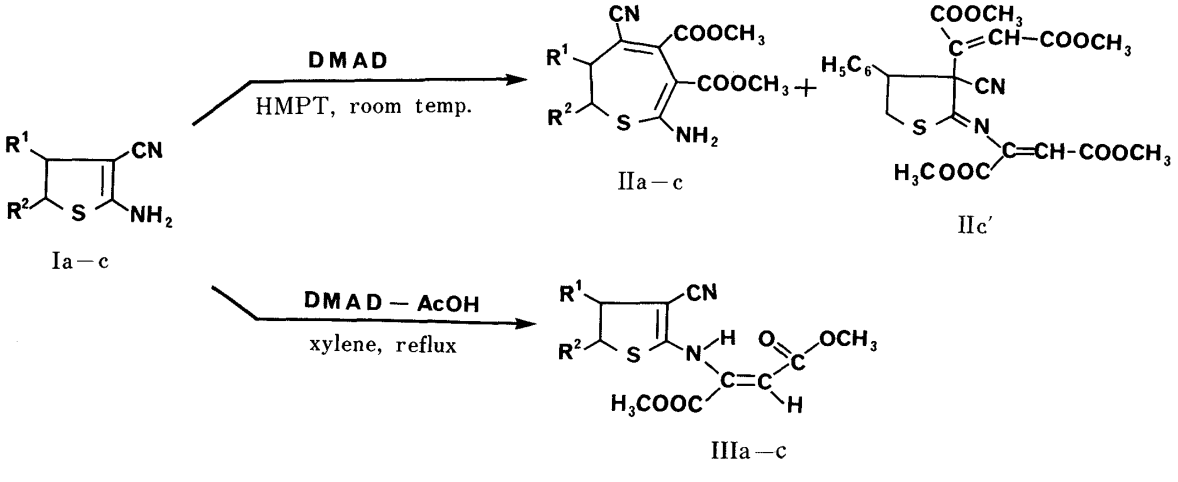
The reactions of 2-amino-3-cyano-4,5-dihydrothiophene (Ia) and 2-amino-3-cyano-5-methyl-(or 4-phenyl)-4,5-dihydrothiophene (Ib or Ic) with dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate in dimethyl sulfoxide (DMSO) or hexamethylphosphoric triamide gave the corresponding dimethyl(or methyl) 2-amino-5-cyano-6,7-dihydrothiepin-3,4-dicarboxylate(or 3-carboxylate) (IIa—c or IVa—c). Compounds Ia—c reacted with DMAD in refluxing xylene to give the corresponding dimethyl α-(3-cyano-4,5-dihydro-2-thienylamino)fumarates (IIIa—c).

Keywords——dimethyl acetylenedicarboxylate; methyl propiolate; 2-amino-3-cyano-4,5-dihydrothiophene; 2,3-dihydrothiepin; ring expansion

Cyclic enamines react with activated acetylenes to give the products of ring expansion with the insertion of two carbons in the rings.[2] In the previous paper,[3] we showed that ethyl 2-amino-3-cyano-4,5-dihydropyrrole-1-carboxylates behave as cyclic enamines toward acetylenic esters to form the corresponding ethyl 2-amino-5-cyano-6,7-dihydro-1*H*-azepine-1-carboxylates. Reinhoudt *et al.*[2e] reported that enamines of tetrahydrothiophen-3-ones react with dimethyl acetylenedicarboxylate (DMAD) to provide the corresponding dihydrothiepins. We examined the reactions of 2-amino-3-cyano-4,5-dihydrothiophenes (Ia—c)[4] with acetylenic esters to see whether or not Ia—c behave as cyclic enamines (Chart 1).



a: $R^1 = R^2 = H$ b: $R^1 = H$, $R^2 = CH_3$ c: $R^1 = C_6H_5$, $R^2 = H$

Chart 1

When a mixture of 2-amino-3-cyano-4,5-dihydrothiophene (Ia) and DMAD in hexamethylphosphoric triamide (HMPT) or dimethyl sulfoxide (DMSO) was stirred at room temperature for 24 h, dimethyl 2-amino-5-cyano-6,7-dihydrothiepin-3,4-dicarboxylate (IIa) was obtained in *ca.* 40% yield. On the other hand, the reaction of Ia with DMAD in refluxing xylene afforded a small amount of dimethyl α-(3-cyano-4,5-dihydro-2-thienylamino)fumarate (IIIa, 10%). When acetic acid was added, IIIa was obtained in somewhat higher yield (16%).

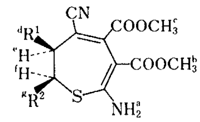
Both IIa and IIIa were proved to be 1 : 1 adducts of Ia to DMAD on the basis of the results of elemental analysis and the mass spectra (MS) of IIa and IIIa. The infrared (IR) spectrum of IIa displayed bands due to an amino group at 3440 and 3290 cm^{-1}, a conjugated cyano group at 2200 cm^{-1}, and carbonyl groups at 1720 and 1675 cm^{-1}. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed two three-proton singlets at δ 3.52 and 3.70 indicative of methoxycarbonyl groups, and a pair of two-proton triplets at δ 2.68 and 3.55 assignable to the protons of C_6 and C_7. On the basis of these data, IIa was assigned as dimethyl 2-amino-5-cyano-6,7-dihydrothiepin-3,4-dicarboxylate. The IR spectrum of IIIa exhibited a conjugated cyano band at 2190 cm^{-1}, and two bands at 1735 and 1678 cm^{-1} indicative of carbonyl groups. The absorption band at 1678 cm^{-1} suggested the presence of hydrogen bonding between the ester carbonyl and an amino group. The ^{1}H-NMR spectrum showed a broad singlet at δ 9.86 (1H) attributable to an amino proton. The olefinic proton appeared as a singlet at δ 5.68. This position is very similar to those of the known aminofumarates.[5] Therefore, IIIa was assigned as the fumarate derivative. In a similar manner, the reaction of 2-amino-3-cyano-5-methyl(or 4-phenyl)-4,5-dihydrothiophene (Ib or Ic) with DMAD in refluxing xylene gave the corresponding fumarate (IIIb or IIIc). In HMPT, the corresponding dihydrothiepin (IIb or IIc) was formed. In the case of Ic, IIc′ was formed as a by-product besides IIc. The structure assignments of IIb, c and IIIb, c were based on the satisfactory elemental analyses and the spectral data. The mass spectrum (M^+: *m*/*z* 486) and the results of elemental analysis of IIc′ indicated that this compound had been formed from one molecule of Ic and two molecules of DMAD. Its IR spectrum exhibited a very weak nonconjugated cyano band at 2240 cm^{-1} and carbonyl bands at 1710, 1725 and 1750 cm^{-1}, and no band due to an amino group was observed. The ^{1}H-NMR spectrum showed four three-proton singlets at δ 3.70, 3.73, 3.78 and 3.86 assignable to methoxycarbonyl groups and

TABLE I. Dimethyl(or Methyl) 2-Amino-5-cyano-6,7-dihydrothiepin-3,4-dicarboxylates(or 3-carboxylates) (IIa—c and IVa—c)

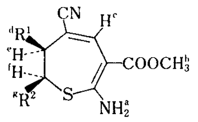
Compd. No.	mp[a] (°C)	Yield (%)	Appearance (Colorless)	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	147	41	Prisms	$C_{11}H_{12}N_2O_4S$	49.25	4.51	10.44
					(49.25	4.53	10.26)
IIb	152	45	Prisms	$C_{12}H_{14}N_2O_4S$	51.06	4.96	9.93
					(51.37	5.12	9.82)
IIc	166—167	24	Prisms	$C_{17}H_{16}N_2O_4S$	59.29	4.68	8.13
					(58.94	4.59	8.05)
IVa	127—128	31	Columns	$C_9H_{10}N_2O_2S$	51.41	4.79	13.32
					(51.54	4.81	13.08)
IVb	150—152	35	Columns	$C_{10}H_{12}N_2O_2S$	53.57	5.39	12.49
					(53.38	5.39	12.40)
IVc	173—174	30	Prisms	$C_{15}H_{14}N_2O_2S$	62.93	4.93	9.79
					(62.86	4.86	9.68)

[a] All compounds were recrystallized from CH_2Cl_2–petr. benzin.

Table II. Spectral Data for IIa—c and IVa—c



IIa—c



IVa—c

a: $R^1=R^2=H$
b: $R^1=H,\ R^2=CH_3$
c: $R^1=C_6H_5,\ R^2=H$

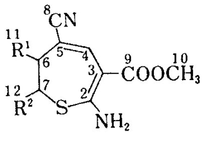
Compd. No.	IR ν_{max}^{KBr} cm^{-1}			^{1}H-NMR spectra (ppm) in DMSO-d_6 solution (J in Hz)							MS m/z (M^+)
	NH_2	CN	CO	$H^{a,a)}$	H^b	H^c	H^d	H^e	H^f	H^g	
IIa	3440 3290	2200	1720 1675	8.67 (br s)	3.70 (s)	3.52 (s)	2.68 (t)		3.55 (t)		268
								(J=7)			
IIb	3400 3280	2200	1715 1670	8.52 (1H) 8.78 (1H) (br s)	3.69 (s)	3.52 (s)	2.32 (dd)	2.76 (dd)	3.91— 4.40 (m)	1.38 (d)	282
						($J_{d,e}$=14, $J_{d,f}$=9, $J_{e,f}$=5, $J_{f,g}$=7)					
IIc	3400 3260	2200	1720 1675	8.78 (br s)	3.68 (s)	3.58 (s)	7.33 (s)	4.04— 4.33 (m)	3.17—4.02 (m)		344
IVa	3360 3200	2190	1640	8.81 (br s)	3.65 (s)	7.18 (t) (J=1)	2.64—2.93 (m)		3.06—3.29 (m)		210
IVb	3360 3200	2190	1660	8.80 (br s)	3.63 (s)	7.15 (t) (J=1)	2.56—2.98 (m)		3.48— 3.84 (m)	1.33 (d) (J=7)	224
IVc	3350 3220	2190	1660	8.90 (br s)	3.70 (s)	7.39 (d) (J=1)	7.15— 7.35 (m)	4.04— 4.33 (m)	3.11—3.38 (m)		286

Abbreviations: br s, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; t, triplet. *a*) Disappeared on treatment with D_2O; amine ($-NH_2$)proton.

two one-proton singlets at δ 5.53 and 5.96 attributable to olefinic protons, in addition to signals due to five protons of the 4-phenyl group and three protons of C_4, C_5. On the basis of these data, IIc′ was tentatively assigned as dimethyl 2-[[3-cyano-4,5-dihydro-3-(3-methoxy-1-methoxycarbonyl-3-oxopropen-1-yl)-4-phenyl-2-(3*H*)-thienylidene]amino]-2-butenedioate, but its stereochemistry was not established.

Subsequently, when a mixture of Ia—c and methyl propiolate in DMSO was heated at 80—85 °C, the corresponding methyl 2-amino-5-cyano-6,7-dihydrothiepin-3-carboxylates (IVa—c) were obtained. These reactions proceeded through the same orientation of addition as in the case of other enamines.[2a,3,6)] The structures of IVa—c were confirmed by the analytical (Table I) and spectral (Tables II and III) data. The ^{13}C nuclear magnetic resonance (^{13}C-NMR) spectra showed signals due to four olefinic carbons. The C_3 olefinic carbons corresponding to the β-carbon of an enamine, like those of other enamines,[3,7)] were shielded by the amino groups at C_2 in IVa—c. The signals due to C_3 appeared as singlets, whereas the signals due to C_4 appeared as doublets. In the ^{1}H-NMR spectra, the proton signals at C_4 in IVa and IVb were observed as triplets, while that of IVc was observed as doublet. The results suggest that the methoxycarbonyl groups are attached to C_3 in IVa—c. The formation of IIa—c and IVa—c can be rationalized in terms of cycloaddition of acetylenic esters to Ia—c to give the intermediates, 2-thiabicyclo[3.2.0]hept-6-enes (A), which undergo ring expansion to form IIa—c and IVa—c as shown in Chart 2.

Table III. ^{13}C-NMR Chemical Shifts of IVa—c δ (ppm) from TMS in $CDCl_3$

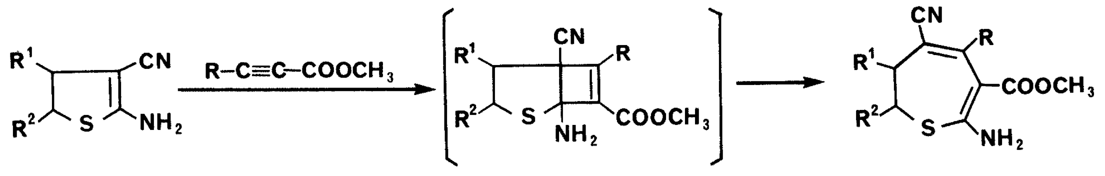


IVa—c

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$

Carbons	2	3	4	5	6	7	8	9	10	11	12
IVa	167.8	92.6	139.7	100.4	29.9	34.3	122.7	169.2	51.3	—	—
	(s)	(s)	(d)	(s)	(t)	(t)	(s)	(s)	(q)		
IVb	164.2	96.2	141.5	103.4	41.2	45.4	122.1	168.2	51.6	—	21.9
	(s)	(s)	(d)	(s)	(t)	(d)	(s)	(s)	(q)		(q)
IVc	168.5$^{a)}$	95.1	140.6	105.4	49.9	38.4	122.1	168.7$^{a)}$	51.8	127.8	—
	(s)	(s)	(d)	(s)	(d)	(t)	(s)	(s)	(q)	128.4	
										128.7	
										140.9	

Abbreviations: d, doublet; q, quartet; s, singlet; t, triplet. *a*) The assignments may be reversed.



Ia—c

A

IIa—c, IVa—c
II: $R=COOCH_3$
IV: $R=H$

a: $R^1=R^2=H$ b: $R^1=H$, $R^2=CH_3$ c: $R^1=C_6H_5$, $R^2=H$

Chart 2

Based on the results described above, it is concluded that Ia—c behave as cyclic enamines toward acetylenic esters.

Experimental

HMPT and DMSO were distilled under reduced pressure and stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or a JASCO A-302 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi R-22 (90 MHz) or a JNM-MH-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained with a JEOL FX-100 (25.1 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-01SG spectrometer.

Reactions of Ia—c with DMAD——i) A mixture of Ia, Ib or Ic (10 mmol) and DMAD (12 mmol) in HMPT (5 ml) was stirred for 24 h at room temperature. The reaction mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as the eluent. The first fraction gave unchanged DMAD. (a) For Ia and Ib: The second fraction gave IIa (1.10 g, 41%) or IIb (1.28 g, 45%). (b) For Ic: The second fraction gave IIc′ (380 mg, 8%), which was recrystallized from CH_2Cl_2–petr. benzin to afford colorless prisms, mp 117—118 °C. *Anal.* Calcd for $C_{23}H_{22}N_2O_8S$: C, 56.78; H, 4.56; N, 5.76. Found: C, 56.79; H, 4.69; N, 5.40. MS *m/z*: 486 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1710, 1725, 1750 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 3.70, 3.73, 3.78, 3.86 (each 3H, s, 4 × $OC\underline{H}_3$), 3.44—4.14 (2H, m, C_5-H), 4.57 (1H, dd, $J=6$, 12 Hz, C_4-H), 5.53, 5.96 (each 1H, s, 2 × $>C=C\underline{H}-COOCH_3$), 7.36 (5H, s, aromatic H). The third fraction gave IIc (810 mg, 24%).

ii) A mixture of Ia or Ib (10 mmol) and DMAD (12 mmol) in DMSO (5 ml) was stirred for 24 h at room temperature. After the DMSO had been removed *in vacuo*, the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIa (1.14 g, 43%) or IIb (1.25 g, 44%).

iii) A solution of Ia, Ib or Ic (10 mmol), DMAD (15 mmol), and AcOH (0.5 ml) in xylene (20 ml) was refluxed for

2 h (in the case of Ia and Ib) or 3 h (in the case of Ic). The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with ether–petr. ether (1 : 1) as the eluent. The first fraction gave the unchanged DMAD. The second fraction gave IIIa (420 mg, 16%), IIIb (840 mg, 30%) or IIIc (1.47 g, 43%). The third fraction gave IIb (40 mg). Dimethyl α-(3-cyano-4,5-dihydro-2-thienylamino)fumarate (IIIa) was recrystallized from ether–petr. ether to yield yellow needles, mp 57—58 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.96; H, 4.55; N, 10.12. MS *m/z*: 268 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200 ($>$NH), 2190 (CN), 1678, 1735 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 2.87—3.11 (2H, m, C_4-H), 3.23—3.53 (2H, m, C_5-H), 3.79, 3.89 (each 3H, s, $2\times OC\underline{H}_3$), 5.68 (1H, s, $>C=C\underline{H}-COOCH_3$), 9.86 (1H, br s, $>$NH). Dimethyl α-(3-cyano-4,5-dihydro-5-methyl-2-thienylamino)fumarate (IIIb) was recrystallized from ether–petr. ether to give yellow columns, mp 87—88 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.06; H, 4.96; N, 9.93. Found: C, 51.20; H, 5.11; N, 9.91. MS *m/z*: 282 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3200 ($>$NH), 2190 (CN), 1685, 1735 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 1.43 (3H, d, $J=7$ Hz, C_5-$C\underline{H}_3$), 2.62 (1H, dd, $J=14.5$, 5.5 Hz, C_4-H), 3.10 (1H, dd, $J=14.5$, 7.7 Hz, C_4-H), 3.60—4.02 (1H, m, C_5-H), 3.76, 3.86 (each 3H, s, $2\times OC\underline{H}_3$), 5.66 (1H, s, $>C=C\underline{H}-COOCH_3$), 9.83 (1H, br s, $>$NH). Dimethyl α-(3-cyano-4,5-dihydro-4-phenyl-2-thienylamino)fumarate (IIIc) was recrystallized from CH_2Cl_2–petr. benzin to give yellow prisms, mp 115—116 °C. *Anal.* Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.36; H, 4.60; N, 8.07. MS *m/z*: 344 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3280 ($>$NH), 2190 (CN), 1680, 1735 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 3.23 (1H, dd, $J=11$, 7 Hz, C_5-H), 3.70 (1H, dd, $J=11$, 8 Hz, C_5-H), 3.78, 3.85 (each 3H, s, $2\times OC\underline{H}_3$), 4.29—4.53 (1H, m, C_4-H), 5.73 (1H, s, $>C=C\underline{H}-COOCH_3$), 7.35 (5H, s, aromatic H), 9.98 (1H, br s, $>$NH).

Reactions of Ia—c with Methyl Propiolate——A mixture of Ia, Ib or Ic (10 mmol) and methyl propiolate (15 mmol) in DMSO (10 ml) was heated at 80—85 °C for 8 h (in the case of Ia and Ib) or 24 h (in the case of Ic) with stirring. The DMSO was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to furnish IVa, IVb or IVc in the yields shown in Table I.

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References

1) Part VI: T. Matsuda, K. Yamagata, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, **33**, 937 (1985).
2) *a)* M. E. Kuehne, "Enamines: Synthesis, Structure, and Reactions," ed. by A. G. Cook, Marcel Dekker, New York, 1969, Chapter 8; *b)* G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963); *c)* K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963); *d)* C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28**, 3134 (1963); *e)* D. N. Reinhoudt and C. G. Leliveld, *Tetrahedron Lett.*, **1972**, 3119; *f)* D. N. Reinhoudt and C. G. Kouwenhouven, *ibid.*, **1973**, 3751.
3) H. Matsunaga, M. Sonoda, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, **32**, 2596 (1984).
4) K. Yamagata, Y. Tomioka, M. Yamazaki, T. Matsuda, and K. Noda, *Chem. Pharm. Bull.*, **30**, 4396 (1982).
5) *a)* A. Srinivasan and A. D. Broom, *J. Org. Chem.*, **44**, 435 (1979); *b)* H. Biere, C. Herrmann, and G. A. Hoyer, *Chem. Ber.*, **111**, 770 (1978); *c)* H. Bière and W. Seelen, *Justus Liebigs Ann. Chem.*, **1976**, 1972, and references cited therein.
6) *a)* M. Lin and V. Snieckus, *J. Org. Chem.*, **36**, 645 (1971); *b)* N. Anghelide, C. Draghici, and D. Răileanu, *Tetrahedron*, **30**, 623 (1974); *c)* H. Wamhoff and J. Hartlapp, *Chem. Ber.*, **109**, 1969 (1976).
7) *a)* H. Junek, P. Wibmer, and B. Thierrichter, *Synthesis*, **1977**, 560; *b)* H. Wamhoff, "Lectures in Heterocyclic Chemistry," Vol. V, ed. by R. N. Castle and S. W. Schneller, Heterocorporation, Orem, Utah, 1980, pp. 61—71.