Addition Reactions of Acetylenic Esters with Monosubstituted Thioureas

By **Libero Italo Giannola** and **Salvatore Palazzo,*** Istituto di Chimica Farmaceutica Applicata, Università di Palermo, Via Archirafi 32, Palermo, Italy
Pasquale Agozzino and **Liliana Lamartina,** Istituto di Chimica Organica, Facoltà di Farmacia, Università di Palermo, Italy
Leopoldo Ceraulo, Istituto di Chimica Farmaceutica e Tossicologica, Università di Palermo, Via Archirafi 32, Palermo, Italy

Monoalkyl-substituted thioureas react with dimethyl acetylenedicarboxylate to give, in a good yield, two different dihydrothiazinones, and not one compound only as has been claimed previously. The structures of the adducts were assigned on the basis of i.r. and ^{1}H n.m.r. spectroscopy, and mass spectrometry.

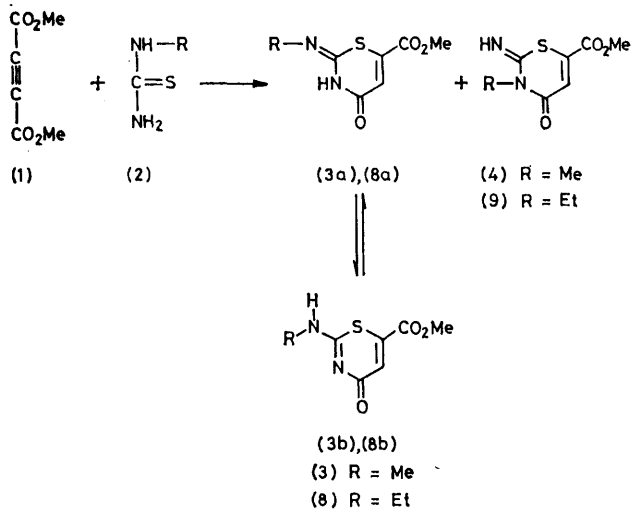
EARLIER papers [1] from these laboratories have described the use of substituted thioureas in the syntheses of 1,3-thiazines. A survey of the literature revealed that Lown and Ma,[2] using n.m.r. and mass spectrometry, assigned the dihydrothiazinone ring structure to the products of the reaction between dimethyl acetylenedicarboxylate (DAD) (1) and thioureas (2). The reported data of such adducts and their perhydro-derivatives conclusively indicate a dihydrothiazinone ring, including the chemical evidence of Winterfeldt *et al.*[3] However, we were very surprised that in the addition reaction of DAD to *N*-methylthiourea, the presence of a methyl group could lead to a single product.

[1] (*a*) S. Palazzo and G. Lombardo, *Gazzetta*, 1963, **93**, 207; (*b*) S. Palazzo, L. I. Giannola, and S. Caronna, *Atti Accad. Sci. Lett. Arti, Palermo*, 1974, **33** (**IV**), 421.

[2] J. W. Lown and J. C. N. Ma, *Canad. J. Chem.*, 1967, **45**, 939.

[3] (*a*) E. Winterfeldt and J. M. Nelke, *Chem. Ber.*, 1967, **100**, 3671; (*b*) E. Winterfeldt, *ibid.*, 1967, **100**, 3679.

Consequently, we have repeated the reaction under the same experimental conditions.[2]



SCHEME 1 Reaction of DAD with monosubstituted thioureas

RESULTS AND DISCUSSION

In our experiments, as we expected, two products in nearly equimolecular amounts were obtained when *N*-methylthiourea reacted with DAD (Scheme 1). The two products (3) and (4) were separable by t.l.c. with a large R_F difference (0.18), using the same eluant as ref. 2. Compounds (3) and (4) were also separable by fractional crystallization and had very different melting points: (3) m.p. 280—281 °C, (4) m.p. 170—172 °C. The analytical and molecular-weight data showed that (3) and (4) were isomers. The mass spectra of the two isomers were closely similar and both showed the main fragmentation process of the dihydrothiazinone ring structure (Scheme 2).[2] Additional confirmation is provided by the close similarity of the cleavage modes of (3) and (4) with all the characteristic features upon electron impact shown by the dihydrobenzothiazinones, for which an unequivocal assignment is described.[4,5] Therefore (3) and (4) differ only in the position of the methyl group.

The ^{1}H n.m.r. spectrum of (3) [$(CD_3)_2SO$] (Table 1) shows a singlet at δ 3.70 (3 H, CO_2Me) and a doublet at δ 3.10 (3 H) (*J* 5 Hz) that collapses to a singlet after exchange with D_2O; this is consistent with an NHMe group. Therefore, for (3) this result is good evidence for the structure [(3a) ⟷ (3b)], with >90% present as the tautomeric form (3b) [<10% of the tautomer (3a) based on the singlet at δ 3.08].

Confirmation of structure (3) is given by methylation. When (3) is allowed to react with methyl iodide, it gives a dimethyl derivative (5) (Table 1), which is different from the adduct (6) obtained by reacting *NN'*-dimethylthiourea with DAD. A peak at *m/e* 170 (4%) was found in the high-resolution mass spectrum of (5) corresponding to loss of NMe_2 from the molecular ion. This spectrum is also consistent with the fragmentation patterns shown in Scheme 2.

Compound (4) must be a positional isomer of (3) and it is assigned the structure shown; its ^{1}H n.m.r. spectrum ($CDCl_3$) exhibits a singlet at δ 3.80 (3 H) for the CO_2Me group and a singlet at δ 3.30 (3 H) assigned to the methyl of the endocyclic nitrogen. Compound (4) is identical to that which Winterfeldt *et al.*[3a] obtained by methylation of the thiourea–DAD adduct (7).

I.r. spectra (Table 1) are diagnostic in assigning the two structures. The i.r. spectrum of (3) shows the absorption of a strongly polar C:N double bond at 1 545 cm^{-1}. This band, characteristic of an N·C:N·C:O group, is absent in the spectrum of (4), in accord with the assigned structures.

Lown and Ma assigned the structure of their sole product using ^{1}H n.m.r. spectroscopy. While their data in $CDCl_3$ are consistent with those of our compound (4), they assigned to the product structure (3a), based on a hypothetical splitting (*J* 5 Hz), due to the protonation in trifluoroacetic acid of the basic exocyclic nitrogen. They also described a similar splitting of the exocyclic NMe signal in the n.m.r. spectrum (in trifluoroacetic acid) of the *NN'*-dimethylthiourea–DAD adduct (6). We recorded ^{1}H n.m.r. spectra of pure samples of (3), (4), and (6) in trifluoroacetic acid and never observed splitting, but only sharp singlets for each methyl group.

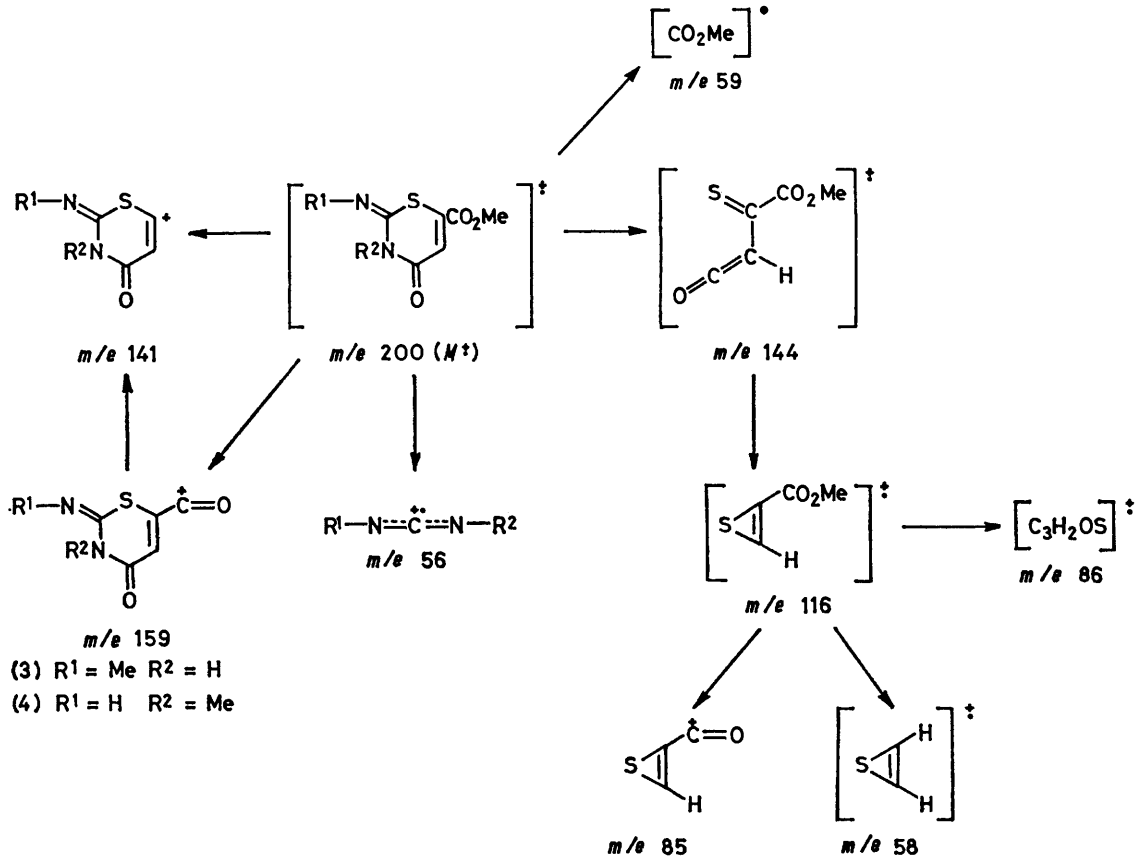
The only acceptable explanation for these discrepancies is that Lown and Ma worked on an equimolar mixture of the two isomers. Their 'compound' has m.p. 253—254 °C. We checked that the crude product of the reaction melted at 253—254 °C when recrystallized twice from methanol, a solvent unsuitable for separation of the two isomers. While (3) is almost insoluble in chloroform, (4) is very soluble; and both are soluble in trifluoroacetic acid. This means that when recording ^{1}H n.m.r. spectra, they used a chloroform solution containing only (4) and a trifluoroacetic acid solution containing both compounds. Thus the ^{1}H n.m.r. spectrum of our reaction mixture in trifluoroacetic acid showed two singlets for the two NMe groups separated by 5 Hz, of similar intensity because the mixture was nearly equimolar: this is the 'doublet' of Lown and Ma. While the signals of the ester methyls overlapped perfectly, and thus appear as one signal, they surprisingly failed to record that the signals of the two vinyl protons were also separated by 5 Hz.

We have also studied the reaction between other asymmetric thioureas and DAD and found that when *N*-ethylthiourea is reacted with DAD, two isomers (8) (m.p. 188—190 °C) and (9) (m.p. 161—162 °C) are obtained (ratio *ca.* 2.5 : 1). These two isomers are correlated, both by R_F values and i.r. and u.v. spectra, with (3) and (4) respectively. The ^{1}H n.m.r. spectrum of (8) shows a multiplet centred at δ 3.55 (2 H, $NHCH_2CH_3$)

[4] H. Boshagen, W. Geiger, H. Hulpke, and C. Wünsche, *Chem. Ber.*, 1971, **104**, 3757.

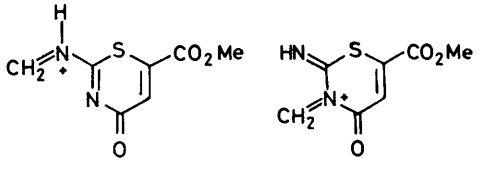
[5] L. Ceraulo, P. Agozzino, M. Ferrugia, and L. I. Giannola, 4th National Congress of Mass Spectrometry, Catania, 12—14 September 1977, Italy.

which becomes a quartet when exchanged with D_2O. These data are consistent with the structure (8a). The ^1H n.m.r. spectrum of (9) is consistent with the structure shown.



SCHEME 2 Mass-spectral fragmentation of adducts (all transitions shown are metastable-supported)

Mass spectrometry is also useful in distinguishing the two kinds of structures (3a) and (8a) and (4) and (9). Mass spectra of (8) and (9) showed a fragment corresponding to $[M - Me]^+$ which is much more abundant for (8) (80%) than (9) (4%). This is in agreement with the comparatively higher stability of the ion (10)



(10) (11)

compared with (11). A careful survey of the mass spectra of (3) and (4) showed a similar behaviour for the $[M - H]^+$ ion of (3) (1.5%) compared with (4) (<0.2%).

In conclusion, when DAD reacts with monoalkylthioureas (at least for small alkyl substituents), the two expected dihydrothiazinone isomers are formed in comparable amounts.

EXPERIMENTAL

M.p.s were determined on a Büchi–Tottoli capillary apparatus. I.r. spectra were recorded on a Perkin-Elmer 157 i.r. spectrophotometer as Nujol mulls, and u.v. spectra for ethanolic solutions with a Perkin-Elmer model 200 spectrophotometer. ^1H N.m.r. spectra were recorded on Varian A-60 (probe temperature 40 °C) and JEOL C-60H (probe temperature 25 °C) instruments with tetramethylsilane as internal standard. Low and high resolution mass spectra were run on a JEOL-JMS-01SG-2 double-focusing mass spectrometer operating with an electron-beam energy of 75 eV and 10 kV accelerating voltage. Exact mass measurements, performed at 15 000 resolving power, were carried out to an accuracy of ±10 p.p.m. of the theoretical values. The detailed mass-spectra are deposited as Supplementary Publication No. SUP 22316 (2 pp.).* Thin-layer chromatography for confirming compound purity utilized 0.25-mm silica gel plates (Merck) with fluorescent indicator, and ethyl acetate–benzene (7 : 3) or methanol–ethyl acetate (2.5 : 97.5) solvent systems.

M.p.s, crystallization solvents, yields, and analytical data are given in Table 2.

Preparation of Methyl 2-Alkylimino-4-oxo-3,4-dihydro-2H- and 2-Alkylamino-4-oxo-4H-1,3-thiazine-6-carboxylates (3) *and* (8) *and Methyl 3-Alkyl-2-imino-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylates* (4) *and* (9).—A solution of DAD (0.12 mol) in warm methanol (50 ml) was added to a stirred

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue.

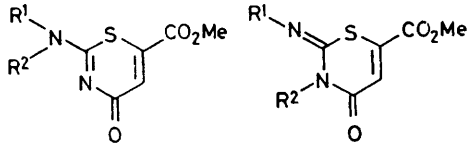
methanolic solution of the appropriate thiourea (0.1 mol). In a few minutes crystals separated, and the reaction set aside overnight. The resulting crude mass was extracted with benzene (3 × 40 ml), the benzene-soluble residue was washed with warm chloroform (2 × 10 ml), and recrystallized from methanol. Two recrystallizations were sufficient to produce an analytically pure sample of (3) or (8). The benzene extracts were combined and evaporated off and after cooling a white product separated. Two recrystallizations from methanol were sufficient to produce an analytically pure sample of (4) or (9).

Preparation of Methyl 2-(NN-*Dimethylamino*)-4-*oxo*-1,3-*thiazine*-6-*carboxylate* (5).—To a solution of (3) (0.01 mol) in boiling absolute methanol (100 ml) was added dropwise with stirring a methanolic solution (20 ml) of sodium methoxide (0.02 g-atom of sodium). The mixture was cooled to 0 °C and filtered to yield the sodium salt of (3) (0.007 mol). A solution of the sodium salt of (3) (0.005 mol) in absolute methanol (20 ml) and methyl iodide (0.05 mol) were refluxed for 5 h, the mixture poured into water and the resulting oil separated by decantation. The oil was dissolved in methanol and the alcoholic solution poured into water giving crude (5) (0.001 5 mol). Two crystallizations from methanol–water (1 : 1) gave white crystals of (5), m.p. 135—136 °C.

[7/1912 *Received*, 1*st November*, 1977]

TABLE 1

Spectroscopic data for thiourea–DAD adducts



Compound	R^1	R^2	R^1	R^2	I.r. (cm^{-1}) NH	ester CO	amide CO	NC=NCO	U.v. (nm)	^{1}H N.m.r. (δ) Vinyl (1H,s)	CO_2Me (3H,s)	NR^1	NR^2	Solvent
(3)	Me	H			3 150	1 710	1 685	1 545	288	6.60	3.70	3.10 (3 H, d, *J* 5 Hz) [a]	9.80 (1 H, broad) [b]	$(CD_3)_2SO$
										7.30	4.05	3.55 (3 H, s)		CF_3CO_2H
(4)			H	Me	3 250	1 720	1 680		308	6.80	3.80	7.60 (1 H, broad) [b]	3.30 (3 H, s)	$CDCl_3$
										6.62	3.78	10.28 (1 H, sharp) [b]	3.18 (3 H, s)	$(CD_3)_2SO$
										7.38	4.05		3.63 (3 H, s)	CF_3CO_2H
(5)	Me	Me				1 700	1 678	1 560	298	6.98	3.90	3.25 (3 H, s)	3.50 (3 H, s)	$CDCl_3$
(6)			Me	Me		1 710	1 650		310	7.42	4.05	3.52 (3 H, s)	3.58 (3 H, s)	CF_3CO_2H
(7)	H	H			3 240	1 710	1 680	1 560	278	6.60	3.76	9.50 (2 H, broad) [b,c]		$(CD_3)_2SO$
(8)	Et	H			3 150	1 705	1 685	1 545	292	6.60	3.80	3.55 (2 H, m, CH_2CH_3) [d] 1.20 (3 H, t, *J* 7 Hz, CH_2CH_3)	9.70 (1 H, broad) [b]	$(CD_3)_2SO$
(9)			H	Et	3 250	1 705	1 675		310	6.60	3.75	9.95 (1 H, sharp) [b]	3.77 (2 H, q, *J* 7 Hz, CH_2CH_3) 1.15 (3 H, t, *J* 7 Hz, CH_2CH_3)	$(CD_3)_2SO$

[a] With D_2O collapses to a singlet. [b] Exchangeable with deuterium oxide. [c] For these protons Lown and Ma reported a signal at δ 6.69 (2 H) in the same solvent. [d] With D_2O becomes quartet (*J* 7 Hz).

TABLE 2

Physical data for thiourea–DAD adducts

Compound	Crystallization solvent	M.p. (°C)	Yield (%)	Molecular weight (by mass spectrometry)	Formula	Analysis (%) Found C	H	N	S	Required C	H	N	S
(3)	Methanol	280—281	43	200	$C_7H_8N_2O_3S$	42.15	3.9	14.1	16.25	42.00	4.03	14.00	15.99
(4)	Methanol	170—172	38	200	$C_7H_8N_2O_3S$	42.2	3.9	14.15	16.2	42.00	4.03	14.00	15.99
(5)	Methanol–water (1 : 1)	135—136	25	214	$C_8H_{10}N_2O_3S$	44.95	4.6	13.15	15.1	44.86	4.71	13.08	14.94
(6)	Methanol	160—161	82	214	$C_8H_{10}N_2O_3S$	45.0	4.5	13.15	15.1	44.86	4.71	13.08	14.94
(7)	Acetic acid	275 (decomp.)	70	186	$C_6H_6N_2O_3S$	38.9	3.2	15.1	17.35	38.72	3.25	15.05	17.19
(8)	Methanol	188—190	54	214	$C_8H_{10}N_2O_3S$	44.95	4.6	13.1	15.15	44.86	4.71	13.08	14.04
(9)	Cyclohexane	161—162	22	214	$C_8H_{10}N_2O_3S$	45.0	4.55	13.25	15.15	44.86	4.71	13.08	14.04