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STRUCTURE OF PRODUCTS OF ADDITION OF THIOSEMICARBAZIDES AND THIOSEMICARBAZONES TO ACETYLENEDICARBOXYLIC ACID AND ITS DIMETHYL ESTER

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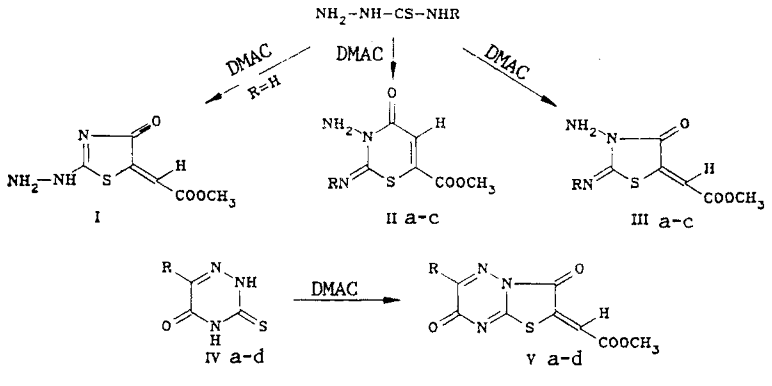
Addition of 1, 1-di-, 1, 4-di-, and 1, 1, 4-trisubstituted thiosemicarbazides to acetylenedicarboxylic acid and its dimethyl ester affords 2-hydrazono-4-oxo-1, 3-thiazolidine-$\Delta^{5,\alpha}$-acetic acids, while 4-monosubstituted thiosemicarbazides give 2-imino-3-amino-1, 3-thiazolidin-4-ones.

Addition of thiosemicarbazides to acetylenedicarboxylic acids affords a variety of heterocyclic systems, but information on their structure is contradictory.

The product of the reaction of thiosemicarbazide with dimethyl acetylene-dicarboxylate (DMAC) has been assigned [1] the 1, 3-thiazoline structure (I).

The products of the reactions of 4-monosubstituted thiosemicarbazides with DMAC have been assigned [2] the 1,3-thiazine structure (II), although according to [3] these compounds are the 3-amino-1, 3-thiazolidin-4-ones (III). It was reported in [4] that DMAC reacts with 6-substituted-3-thioxo-5-oxo-1, 2, 4-triazines (IV) (cyclic analogs of thiosemicarbazides) to give the 1, 3-thiazolidin-4-ones (V) rather than the 1, 3-thiazines [5]. The structure of (V) was proved by ^{13}C NMR spectroscopy.



II, III a $R=CH_3$, b $R=CH_2CH=CH_2$, c $R=C_6H_5$; IV, V a $R=H$, b $R=CH_3$, c $R=C_6H_5$, d $R=C_6H_5CH_2$

It has previously been shown by X-ray diffraction examination of the thiazolidines obtained by reaction of thioureas with DMAC [6] that donor—acceptor interactions are present

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TABLE 1. Properties of 2-Hydrazone-4-oxo-1, 3-thiazolidine-$\Delta^{5,\alpha}$-acetic Acids (X), (XII), and (XIV)

Compound	Empirical formula	mp, °C	IR spectra of groups N-H, = C-H, C = O, C = N, C = C (in Nujol, cm^{-1})	PMR spectra, ppm (in DMSO-D$_6$)				Yield %
				R^1, R^2	R^3	R^4, s	=CH, s	
Xa	$C_7H_9N_3O_3S$	280 ... 283	3200, 3120, 3055, 1724, 1672, 1654, 1612	2,50 (s)	12,3 (s)	12,30	6,56	72
Xb	$C_8H_{11}N_3O_3S$	228 ... 230	3215, 3050, 1717, 1703, 1636, 1607	2,50 (s)	12,0 (s)	3,74	6,61	71
Xc	$C_8H_{11}N_3O_3S$	221 ... 223	3078, 1724, 1691, 1632, 1606	2,54 (s)	3,33 (s)	—	6,87	88
Xd	$C_9H_{13}N_3O_3S$	123 ... 124	3078, 1718, 1701, 1625, 1608	2,47 (s)	3,18 (s)	3,76	6,67	72
Xe	$C_{10}H_{13}N_3O_3S$	172 ... 173	3065, 1730, 1680, 1650, 1632, 1603	2,56 (s)	4,48, 5,23, 5,89***	11,40	6,89	67
Xf	$C_{11}H_{17}N_3O_3S$	164 ... 166	3070, 1725, 1680, 1630, 1600	2,47 (s)	0,89, 1,41, 3,73***	—	6,63	67
Xg	$C_{13}H_{13}N_3O_3S$	252 ... 255	3060, 1730, 1720, 1695, 1680, 1630, 1605, 1593, 1500	2,42 (s)	7,33 ... 7,55 (m)	12,04	6,69	86
Xh	$C_{14}H_{15}N_3O_3S$	154 ... 155	3058, 1725, 1712, 1700, 1630, 1615, 1500	2,44 (s)	7,18 ... 7,64 (m)	3,80	6,73	84
Xi	$C_{14}H_{15}N_3O_3S$	202 ... 203	3065, 1720, 1680, 1632, 1600	2,48 (s)	4,92 (c); 7,29 (m)	12,0	6,70	62
Xj	$C_{14}H_{13}N_3O_4S$	230 ... 232	3076, 1745, 1700, 1642, 1630, 1618, 1598, 1580, 1497	2,96 (s)	7,42 ... 8,30 (m)	—	6,81	60
Xk	$C_{15}H_{15}N_3O_4S$	212 ... 214	3065, 1750, 1680, 1646, 1635, 1622, 1600, 1581, 1500	3,08 (s)	7,33 ... 7,62 (m)	3,84	6,98	72
Xl	$C_{11}H_{15}N_3O_3S$	196 ... 198	3058, 1735, 1725, 1692, 1620, 1600	1,54 (6H, m); 2,54*** (4H m);	3,18 (s)	12,0	6,63	82
Xm	$C_{12}H_{17}N_3O_3S$	112 ... 113	3070, 1725, 1700, 1624, 1607	1,50 (6H, m); 2,55*** (4H, m);	3,18 (s)	3,73	6,66	83
Xn	$C_{14}H_{19}N_3O_3S$	61 ... 62	3070, 1725, 1697, 1650, 1630, 1622	1,48 (6H, m); 2,69*** (4H, m);	4,31; 5,00; 5,81***	3,73	6,66	78
Xo	$C_{14}H_{15}N_3O_3S$	187 ... 188	3070, 1730, 1680, 1621, 1607, 1595, 1492	1,08 (t); 3,48 (q) 6,76 ... 7,32 (m)	3,36 (s)	11,90	6,70	82
Xp	$C_{15}H_{17}N_3O_3S$	124 ... 125	3065, 1720, 1702, 1620, 1610, 1599, 1490	1,08 (t); 3,48 (q) 6,80 .. 7,37 (m)	3,37 (s)	3,74	6,72	84
XIIa	$C_{12}H_{11}N_3O_3S$	260 ... 263	3295, 3090, 1705, 1655, 1644, 1600, 1593, 1523, 1495	6,62 ... 7,31 (m); 9,20 (s)	3,29 (s)	—	6,64	72
XIIb	$C_{13}H_{13}N_3O_3S$	140 ... 141	3295, 3060, 1710, 1690, 1666, 1624, 1600, 1500	6,64 ... 7,30 (m); 9,27 (s)	3,29 (s)	3,78	6,69	72
XIIc	$C_{15}H_{15}N_3O_3S$	139 ... 140	3390, 3070, 1705, 1692, 1660, 1630, 1615, 1602, 1590	6,60 ... 7,34 (m); 9,32 (s)	4,43; 5,19; 5,91***	3,80	6,73	69
XIId	$C_{13}H_{11}N_3O_4S$	274 ... 276	3150, 3070, 1723, 1682, 1628, 1608, 1580	6,36 ... 7,89 (m); 11,15 (s)	3,20 (s)	11,90	6,74	79
XIIe	$C_{14}H_{13}N_3O_4S$	193 ... 194	3210, 3070, 1720, 1695, 1645, 1620, 1605, 1583, 1500	7,40 ... 7,96 (m); 11,26 (s)	3,32 (s)	3,78	6,79	63
XIIf	$C_{15}H_{13}N_3O_4S$	233 ... 234	3160, 3060, 1713, 1672, 1642, 1623, 1603, 1577, 1550	7,28 ... 7,90 (m); 11,20 (s)	4,47; 5,19; 5,89***	11,70	6,73	84
XIIg	$C_{16}H_{15}N_3O_4S$	205 ... 206	3205, 3072, 1722, 1696, 1660, 1620, 1609, 1582	7,38 ... 7,98 (m); 11,28 (s)	4,45; 5,16; 5,89***	3,78	6,81	72
XIIh	$C_{11}H_{15}N_3O_5S$	195 ... 196	3230, 3080, 1715, 1709, 1690, 1635, 1622	1,47 (s); 9,98 (s)	3,22 (s)	12,04	6,66	77
XIIi	$C_{12}H_{17}N_3O_5S$	160 ... 161	3185, 3070, 1722, 1706, 1625, 1609	1,43 (s); 10,04 (s)	3,20 (s)	3,77	6,71	76
XIIj	$C_{13}H_{17}N_3O_5S$	225 ... 228	3200, 3095, 3084, 3072, 1715, 1703, 1700, 1680, 1645	1,43 (s); 9,88 (s)	4,35; 5,10; 5,84***	11,90	6,67	82
XIIk	$C_{14}H_{19}N_3O_5S$	144 ... 145	3210, 3100, 3065, 1713, 1700, 1690, 1634, 1618	1,44 (s); 10,10 (s)	4,36; 5,14; 5,84***	3,77	6,74	71
XIVa	$C_7H_7N_3O_3S$	220 ... 222	3080, 3059, 1730, 1678, 1667, 1660, 1622, 1593	1,99 (s); 7,80 (s)	12,40 (s)	12,40	6,55	68
XIVb	$C_9H_9N_3O_5S$	230 ... 233	1733, 1678, 1660, 1620, 1600	3,51 (d) 3,67 (s), 7,80 (t)	12,0 (s)	12,0	6,58	75
XIVc	$C_{10}H_{11}N_3O_5S$	197 ... 199		3,48 (d) 3,63 (s), 7,80 (t)	12,51 (s)	3,74	6,61	73
XIVd	$C_{12}H_{15}N_3O_3S$	240 ... 242	3380, 3140, 3072, 1740, 1707, 1700, 1642, 1619, 1604	1,67 (6H, m); 2,48*** (4H, m)	12,5 (s)	3,74	6,61	72
XIVe	$C_{11}H_{13}N_3O_3S$	243 ... 244	3160, 3070, 1737, 1710, 1680, 1642, 1600	1,63 (6H, m); 2,43*** (4H, m)	11,7 (s)	11,7	6,56	78
XIVf	$C_{13}H_{17}N_3O_3S$	161 ... 162	3066, 1715, 1700, 1840, 1635, 1617, 1592	1,63 (6H, m); 2,52*** (4H, m)	3,26 (s)	3,78	6,70	86

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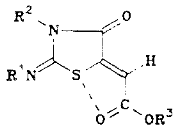
*(Xa), (XIIa, h, j), and (XIVa, b), with decomposition.

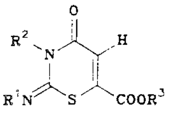
**The spectra of (Xc, e, k) were obtained in $CDCl_3$.

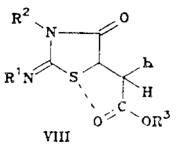
***Centers of multiplets.

in (VI (R^1 = H, R^2 = CH_3) between the sulfur and the oxygen atom of the carbonyl group (the S...O distance is approximately 2.9 Å ($r_S + r_0$ = ~ 3.25 Å)).

This shortened S...O distance is retained in the reduced form (VIII) [7]. It is this property which is clearly responsible for the erroneous conclusions of many workers [2, 8, 9] that the products of the reactions of DMAC with thioureas and thiosemicarbazides have the six-membered structure (VII). In these reports, the magnetic nonequivalence of the CH_2 protons in the PMR spectra was taken as evidence of their incorporation in a six-membered ring.

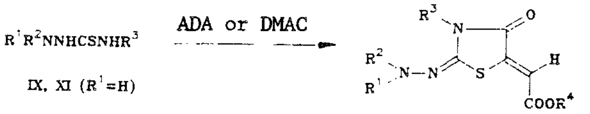

VI


VII

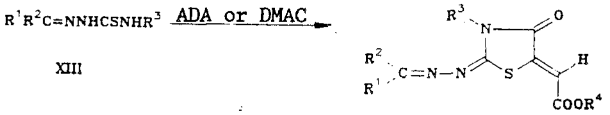

VIII

In order to establish the effects of substituents in the thiosemicarbazide molecule on the course of the reaction, we have carried out the reactions between 1,1-di-, 1,4-di-, 2,4-di-, and 1,1,4-trisubstituted thiosemicarbazides and acetylenedicarboxylic acid (ADA) and DMAC. The reactions were usually carried out in ethanol or methanol, although when the thiosemicarbazide was of low reactivity, water or acetic acid was used as solvent.

On heating equimolar amounts of 1,4-di- or 1,1,4-trisubstituted thiosemicarbazides (IX) and (XI) with ADA or DMAC in alcohol, the thiazolidinones (X) and (XII) were obtained. Similarly, equimolar amounts of the thiosemicarbazones (XIII) and ADA or DMAC gave the 1,3-thiazolidinones (XIV).



xa-p xiia-k(R'=H)

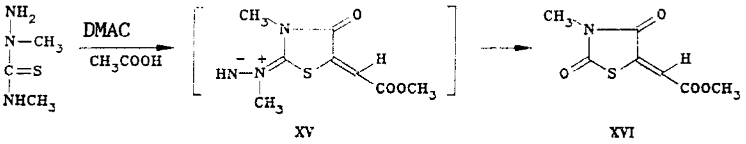


xiv a-f

X a- k $R^1 = R^2 = CH_3$, ℓ-n R^1, $R^2 = (CH_2)_5$, o, p R^1, $R^2 = C_6H_5$; a, b R^3 = H, c, d, f, ℓ, m, o, p $R^3 = CH_3$ g, h $R^3 = C_6H_5$, i, $R_3 = C_6H_5CH_2$, j, k $R^3 = C_6H_5CO$, e,n $R^3 = CH_2CH{=}CH_2$; a, c, e-g, i, j, ℓ, o R^4 = H, b, d, h, k, m, n, p $R^4 = CH_3$; XII a-c $R^1 = C_6H_5$, d-h $R^2 = C_6H_5CO$, g-k R^2 = t-BuO_2C; a, b, d,e, h, i $R^3 = CH_3$, c, f, g, j, k $R^3 = CH_2CH{=}CH_2$; a, d, f, h, j R^4 = H, b, c, e, g, i, k $R^4 = CH_3$; XIV a-c R^1 = H, d-f R^1, $R^2 = (CH_2)_5$; a $R^2 = CH_3$, b, c $R^2 = CH_2COOCH_3$; a-e R^3 = H, f $R^3 = CH_3$: a, b, e R^4 = H, c, d, f $R^4 = CH_3$

These results cast doubt on the structures of the 2-imino-3-amino-1,3-thiazolidin-4-ones (IIIc, d) described in [3], and the structure (II) assigned by other workers [2] to the products of the reaction of 4-substituted thiosemicarbazides with DMAC is just as unlikely. We have repeated this work with 4-methyl- and 4-allylthiosemicarbazides, and have examined the PMR and ^{13}C NMR spectra of the products obtained (see below). Our findings confirm the structure (III) [3].

We have also established that with 2,4-disubstituted thiosemicarbazides, despite the apparent impossibility of S-addition with simultaneous condensation at $N_{(4)}$, no reaction involving $N_{(1)}$ occurred. This is clearly basically due to the low reactivity of 2-substituted thiosemicarbazides towards DMAC. This reaction failed to occur in alcohols or acetonitrile. Only on boiling the reactants in acetic acid was the previously-reported [10] 5-methoxycarbonylmethylene-1,3-thiazolidine-2,4-dione (XVI) obtained, apparently by hydrolysis of the intermediate zwitterionic compound (XV) in the acidic medium:



Consequently, atom $N_{(1)}$ in 1-unsubstituted, 1-mono-, or 1,4-disubstituted thiosemicarbazides is not involved in addition to the triple bond in ADA or DMAC. It appears that the formation of a heterocycle other than a 1,3-thiazolidinone or a 1,3-thiazinone in this reaction can only be expected in special cases. For this to occur, $N_{(1)}$ of the thiosemicarbazide must be more nucleophilic than sulfur, which requires specific substituents, or steric factors must substantially hinder the primary reaction of the alkyne with the sulfur atom.

Conclusions as to the structures of (III), (X), (XII), and (XIV) were made from the values of the $^{13}C-^{1}H$ coupling constants for the products of the reaction of thioureas with DMAC [11], the structures of which were proved by X-ray diffraction. The $^{13}C-^{1}H$ coupling constants between $C_{(7)}$ of the ester group and the vinyl hydrogen are approximately 1 Hz, which is characteristic only of the geminal constant $^{2}J(^{13}C-^{1}H)$ [12], and shows conclusively the presence in the molecule of an exocyclic double bond. The coupling constant between the amide carbonyl $C_{(4)}$ and the vinyl proton is 5-6 Hz in all the compounds examined, corresponding to cis-orientation [12]. In all cases, therefore, trans-addition to the double bond takes place.

A choice between structures (III), (X), and (XIV) was made by examining the coupling constants between the protons in the radical NR^2 and $C_{(2)}$ and $C_{(4)}$ of the five-membered ring. The constants for (X), (XII), and (XIV) of the NR^2 protons with both $C_{(2)}$ and $C_{(4)}$ were 2.0-2.5 Hz, whereas in the case of (III) only interaction with $C_{(2)}$ occurred, with a J value of 9.3-9.7 Hz.

The $^{13}C-^{1}H$ coupling constant thus provided unambiguous proof of the structures of the reaction products.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90 spectrometer (90 MHz) in DMSO-D_6, internal standard TMS, and ^{13}C NMR spectra (standard TMS) and ^{13}N NMR spectra (standard nitromethane) on a Bruker WH-90 (22.62 MHz) in DMSO-D_6. IR spectra were obtained on a Perkin-Elmer 580 B instrument, in Nujol. The progress of the reactions and the purity of the products were followed by TLC on Silufol-254 plates using the eluent system hexane—ethyl acetate (2:1) or ethyl acetate. The required thiosemicarbazides were obtained from the appropriate hydrazines and isothiocyanates. The mixtures of 1,4- and 2,4-disubstituted thiosemicarbazides were separated on a column of silica gel, eluent hexane—ethyl acetate (3:1). The physicochemical properties of the thiosemicarbazides and thiosemicarbazones were in agreement with the reported values [2, 13-15].

The properties of the products are given in Table 1. The elemental analyses for C, H, and N of compounds (X), (XII), and (XIV) were in agreement with the calculated values.

General Method of Preparation of 2-Hydrazono-4-oxo-1,3-thiazolidine-$\Delta^{5,\alpha}$-acetic Acids and Esters (X, XII, XIV). To a solution of 10 mmole of the thiosemicarbazide or thiosemicarbazone in 40 ml of alcohol was added with stirring 11 mmole of acetylenedicarboxylic acid or its dimethyl ester. The mixture was boiled with stirring for 30 min, cooled, and the crystalline solid which separated was filtered off and washed with cold alcohol. The filtrate was evaporated under reduced pressure, and recrystallized from a mixture of ethanol and 2-propanol (1:2).

Compound (Xc). ^{13}C NMR spectrum: 167.0 (COO); 165.4 ($C_{(4)}$); 159.0 ($C_{(2)}$); 141.7 $C_{(5)}$); 116.7 ($C_{(6)}$); 47.6 ppm ($(CH_3)_2N$). ^{15}N NMR spectrum: −241.9 ($N_{(3)}$); −81.0 ($C=N$); −279 ppm [$N(CH_3)_2$].

Compound (XIIc). ^{13}C NMR spectrum: 165.9 (COO); 162.1 ($C_{(4)}$); 141.3 ($C_{(5)}$); 138.2 ($C_{(2)}$); 113.4 ($C_{(6)}$); 146.3; 113.0; 128.7; 119.3 ($C_{i,o,m,p}$ of the phenyl group, respectively); 55.3 (OCH_3); 44.7, 131.3, and 117.6 ppm (CH_2CH and $=CH_2$ carbons of the allyl group).

Compound (XIVf). ^{13}C NMR spectrum: 165.7 (COO); 164.3 ($C_{(4)}$; 156.6 ($C_{(2)}$; 141.9 ($C_{(5)}$); 114.3 ($C_{(6)}$); 172.6 (C_α); 34.9 and 28.1 (C_β and C_β); 27.0 and 26.0 (C_γ and C_γ); 25.1 (C_δ); 29.3 (NCH_3); 52.3 ppm (OCH_3).

Reaction of 2, 4-Dimethylthiosemicarbazide with Dimethyl Acetylenedicarboxylate. 2,4-Dimethylthiosemicarbazide (1.19 g, 10 mmole) was dissolved in 30 ml of glacial acetic acid, and 1.45 g (10.2 mmole) of DMAC added. The solution was stirred for 8 h at 80°C, then evaporated under reduced pressure. The residue was twice treated with alcohol and evaporated to dryness, and recrystallized from alcohol to give 10 g (50%) of colorless crystals of methyl 2, 4-dioxo-1, 3-thiazolidine-$\Delta^{5,\alpha}$-acetate, $C_7H_7NO_4S$, mp 110-111°C. According to [10], mp 111°C. PMR spectrum: 3.08 (3H, s, NCH_3); 3.80 (3H, s, OCH_3); 6.94 ppm (1H, s, = CH).

2-Imino-3-amino-5-methoxycarbonylmethylene-1, 3-thiazolidine-4-ones (IIIa, b) were obtained as described in [3]. Compound (IIIa) ($C_7H_9N_3O_3S$). Yield, 70%, mp 182-183°C; according to [2], mp 188°C, and [3], 179-180°C. PMR spectrum: 3.24 (3H, s, NCH_3); 3.77 (3H, s. OCH_3); 5.33 (2H, s, NH_2); 6.77 ppm (1H, s, =CH). ^{13}C NMR spectrum: 166.8 (COO); 161.8 ($C_{(4)}$); 149.3 ($C_{(2)}$); 140.4 ($C_{(5)}$); 115.6 ($C_{(6)}$); 53.5 (OCH_3); 39.4 ppm (NCH_3).

Compound (IIIb) ($C_9H_{11}H_3O_3S$). Yield 71%, mp 125-126°C; according to [2], mp 125°C. PMR spectrum: 3.76 (3H, s, OCH_3); 4.02-4.15 (2H, m, NCH_2); 5.02 (2H, m, $=CH_2$); 5.37 (2H, s, NH_2); 5.75-6.22 (1H, m, allyl = CH); 6.74 ppm (1H, s, = CH). ^{13}C NMR spectrum:166.7 (COO); 161.8 ($C_{(4)}$); 149.2 ($C_{(2)}$); 140.4 ($C_{(5)}$); 115.8 ($C_{(6)}$); 54.6; 135.8; 117.1 (NCH_2, and allyl =CH and = CH_2); 5.35 ppm (OCH_3).

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