Reaction of 2-Dimethylaminomethylene-1,3-diones with Dinucleophiles. IV. Synthesis of 5,7-Dihydrothiopyrano[3,4-*c*]pyrazol-4(1*H*)-ones, 5*H*-Thiopyrano[4,3-*d*]isoxazol-4(7*H*)-one and 6*H*-Thiopyrano[3,4-*d*]pyrimidin-5(8*H*)-ones

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The reaction of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione with *N*,*N*-dimethylformamide dimethyl acetal gave in good yield 4-dimethylaminomethylene-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (II), which afforded 1-substituted 5,7-dihydrothiopyrano[3,4-*c*]pyrazol-4(1*H*)-ones with aliphatic and aromatic hydrazines, 5*H*-thiopyrano[4,3-*d*]isoxazol-4(7*H*)-one (IV) with hydroxylamine hydrochloride and 2-substituted 6*H*-thiopyrano[3,4-*d*]pyrimidin-5(8*H*)-ones with amidines and guanidines, generally in satisfactory yields. 4-(*t*-Butylhydrazonoformyl)-2*H*-thiopyran-3,5(4*H*,6*H*)-dione was isolated as an intermediate in the reaction of II with *t*-butylhydrazine, whereas formamidine gave with II 4-iminoformyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione as the sole product. The isoxazole IV isomerized easily with sodium methoxide to 3,4,5,6-tetrahydro-5,5-dihydroxy-3-oxo-2*H*-thiopyrano-4-carbonitrile.

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In the preceding papers of the series [1,2,3] we reported the facile reaction of open-chain and cyclic *sym*-2-dimethylaminomethylene-1,3-diones with *N-N*, *N-O* and *N-C-N* dinucleophiles such as hydrazines, hydroxylamine, amidines and guanidine to give 1,5-disubstituted 4-acylpyrazoles, 5-substituted 4-acylisoxazoles and 5-acylpyrimidines, respectively. We now wish to report the reaction of the heterocyclic *sym*-2-dimethylaminomethylene-1,3-dione II with the nucleophiles cited above, in order to obtain new functionalized sulfur heterocycles having a thiopyran ring condensed with important heterocycles such as pyrazole, isoxazole and pyrimidine.

The starting synthon 4-dimethylaminomethylene-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (II) was prepared in good yield by simply stirring at 0° a solution of 2*H*-thiopyran-3,5-(4*H*,6*H*)-dione (I) [4] in *N*,*N*-dimethylformamide dimethyl acetal. As in the case of cyclic *sym*-2-dimethylaminomethylene-1,3-diones previously described [1], the nmr spectrum of II showed two singlets for the dimethylamino group, a feature due to hindered rotation. The reaction of II with aliphatic hydrazines was carried out in satisfactory yields at reflux in alcohols such as methanol and ethanol, generally in the presence of acetic acid, and occurred also when a bulky alkyl group such as *t*-butyl was present as hydrazine substituent, provided that an higher boiling alcohol such as 1-butanol was employed as the solvent.

When the reaction of II with *t*-butylhydrazine was carried out in ethanol with a reduced reflux time, the inter-

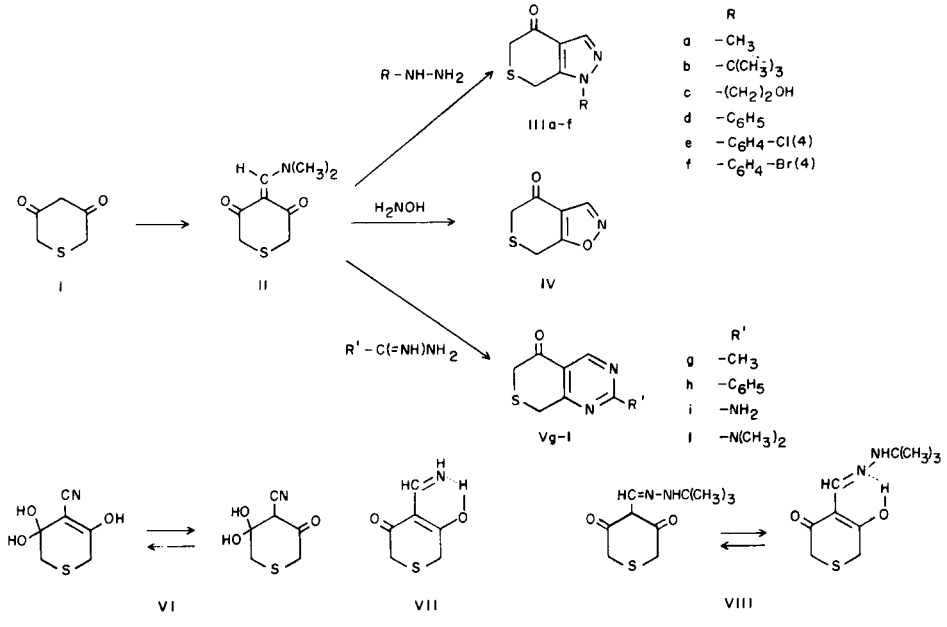
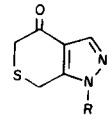


Table I

1-Substituted 5,7-Dihydrothiopyrano[3,4-*c*]pyrazol-4(1*H*)-ones IIIa-f [a]



Formula Number	R	Reflux Time (hours)	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$-CH_3$	1 [b]	66	141 [e]	$C_7H_8N_2OS$	49.98	4.79	16.65
						50.14	4.78	16.92
IIIb	$-C(CH_3)_3$	3 [c]	72	106 [e]	$C_{10}H_{14}N_2OS$	57.11	6.71	13.32
						57.19	6.70	13.60
IIIc	$-(CH_2)_2OH$	1 [d]	74	116 [f]	$C_8H_{10}N_2O_2S$	48.47	5.08	14.13
						48.67	5.14	14.28
IIId	$-C_6H_5$	1 [d]	76	145 [e]	$C_{12}H_{10}N_2OS$	62.59	4.38	12.16
						62.81	4.47	12.40
IIIe	$-C_6H_4$-Cl (4)	1 [d]	80	181 [f]	$C_{12}H_9ClN_2OS$	54.44	3.43	10.58
						54.66	3.51	10.72
IIIf	$-C_6H_4$-Br (4)	1 [d]	77	193 [f]	$C_{12}H_9BrN_2OS$	46.62	2.93	9.06
						46.38	3.11	8.94

[a] All compounds were prepared according to the literature [1], with reflux times and solvents as tabulated. [b] In anhydrous methanol. [c] In anhydrous 1-butanol plus acetic acid. [d] In anhydrous ethanol plus acetic acid. [e] From anhydrous diethyl ether. [f] From ethyl acetate.

Table II

UV, IR and NMR Spectral Data of Compounds IIIa-f

	UV λ max nm (log ε)	IR, cm^{-1}	NMR, δ (Deuteriochloroform)
IIIa	249 (3.92)	1670, 1496, 1440 [a]	3.35 (s, CH_2-5), 3.85 (near s, CH_2-7, CH_3N), 7.90 (s, CH-3)
IIIb	250 (3.96)	1667, 1530, 1470 [a]	1.66 [s, $(CH_3)_3C$], 3.33 (near s, CH_2-5), 4.03 (near s, CH_2-7), 7.87 (near s, CH-3)
IIIc	249 (3.94)	3290, 3115, 1662, 1503, 1446 [b]	3.40 (s, CH_2-5, CH_2-7), 3.76 (t, J = 5, CH_2O), 4.05 (mc, CH_2N), 4.96 (t, J = 5, OH; disappears with deuterium oxide), 7.87 (near s, CH-3) [c]
IIId	258 (4.15)	1670, 1540, 1470, 1403 [a]	3.44 (s, CH_2-5), 3.90 (s, CH_2-7), 7.53 (s, C_6H_5), 8.11 (s, CH-3)
IIIe	228 (4.09) 260 (4.215)	1675, 1530, 1468, 1423, 1408 [b]	3.44 (s, CH_2-5), 3.88 (s, CH_2-7), 7.48 (s, 4 H ar), 8.11 (s, CH-3)
IIIf	232 (4.11) 260 (4.24)	1677, 1540, 1466, 1423, 1409 [b]	3.44 (s, CH_2-5), 3.88 (s, CH_2-7), 7.36 (d, J = 9, 2 H ar 2, 6), 7.67 (d, J = 9, 2 H ar 3,5), 8.10 (s, CH-3)

[a] In chloroform. [b] In potassium bromide. [c] In DMSO-d_6.

mediate VIII could be isolated in moderate yield. This fact suggests that the heterocyclization is proceeding through two steps, a preliminary attack of the most nucleophilic site of the hydrazine on the strongly electrophilic carbon atom of the $=CH-NMe_2$ group with elimination of dimethylamine, followed by the cyclization step.

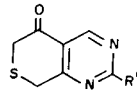
Also with aromatic hydrazines, the reaction of II occurred in good yields by reflux in ethanol solution in the presence of acetic acid.

The structure of pyrazoles IIIa-f (Table I) was ascertained through their spectral data (Table II).

5*H*-Thiopyrano[4,3-*d*]isoxazol-4(7*H*)-one (IV) was pre-

Table III

2-Substituted 6*H*-Thiopyrano[3,4-*d*]pyrimidin-5(8*H*)-ones Vg-l [a]



Formula Number	R'	Yield %	Mp °C	Molecular Formula	Analyses % Calcd./Found C	H	N
Vg	$-CH_3$	24	70 [b]	$C_8H_8N_2OS$	53.31 53.47	4.47 4.48	15.54 15.66
Vh	$-C_6H_5$	66	176 [c]	$C_{13}H_{10}N_2OS$	64.44 64.68	4.16 4.13	11.56 11.71
Vi	$-NH_2$	72	257 dec [c]	$C_7H_7N_3OS$	46.40 46.32	3.89 3.97	23.19 23.00
Vl	$-N(CH_3)_2$	83	143 [d]	$C_9H_{11}N_3OS$	51.66 51.74	5.30 5.30	20.08 20.30

	UV λ max nm (log ε)	IR, cm^{-1} (Chloroform)	NMR, δ (Deuteriochloroform)
Vg	239 (3.87)	1695, 1575, 1552, 1432	2.78 (s, CH_3), 3.56 (s, CH_2-6), 3.97 (s, CH_2-8), 9.17 (s, CH-4)
Vh	291.5 (4.36)	1695, 1567, 1543, 1418	3.55 (s, CH_2-6), 4.02 (s, CH_2-8), 7.54 (mc, 2 H ar *m*, 1 H ar *p*), 8.45 (mc, 2 H ar *o*), 9.30 (near s, CH-4)
Vi	285 (4.205)	3270, 3120, 1665, 1590, 1547, 1500, 1423 [e]	3.52 (s, CH_2-6), 3.79 (s, CH_2-8), 7.63 (broad s, NH_2; disappears with deuterium oxide), 8.69 (s, CH-4) [f]
Vl	308.5 (4.31)	1667, 1582, 1520, 1410	3.28 [s, $(CH_3)_2N$], 3.45 (s, CH_2-6), 3.75 (s, CH_2-8), 8.92 (s, CH-4)

[a] All compounds were prepared according to the literature [3], solvent anhydrous ethanol, reflux time 3 hours. Compounds Vg,i,l were extracted with chloroform, whereas Vh separated by cooling the reaction mixture. Compound Vg was further purified by chromatography on Florisil (diethyl ether) and recrystallization from petroleum ether bp 40-70°, since it contained a little amount of VI. [b] From petroleum ether bp 40-70°. [c] From 95% ethanol. [d] From anhydrous diethyl ether. [e] In potassium bromide. [f] In DMSO-d_6.

pared in satisfactory yield by a previously described procedure [2], namely by refluxing a methanol solution of II and hydroxylamine hydrochloride. The compound IV, as a typical 3-unsubstituted isoxazole carrying moreover an electron-withdrawing substituent in position 4, underwent a facile isomerization with sodium methoxide in the cold to the corresponding 2-cyano-1,3-dione VI. The nitrile VI contained a molecule of water which could not be eliminated by heating owing to decomposition of the product. The nmr spectrum of VI showed that this compound exists as a simple enol, whereas the other carbonyl group is in hydrate form.

2-Substituted 6*H*-thiopyrano[3,4-*d*]pyrimidin-5(8*H*)-ones Vg-l (Table III) were prepared, generally in satisfactory yield, by refluxing an ethanol solution of both II and amidines or guanidines, according to a previously described procedure [3]. When formamidine was employed in this reaction, 4-iminoformyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (VII) was formed as a sole product. Thus, formamidine gave the same result as in the case of other open-chain and cyclic *sym*-2-dimethylaminomethylene-1,3-diones [3]. A little amount of VII was also formed in the reaction of II with acetamidine (see Table III).

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. The ir spectra were taken on a Perkin-Elmer Model 398 spectrophotometer; the nmr spectra were recorded on a Perkin-Elmer Model R-100 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus.

4-Dimethylaminomethylene-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (II).

A solution of I [4] (13 g, 0.1 mole) in *N*,*N*-dimethylformamide dimethyl acetal (24 g, ~0.2 mole) prepared at 0° was stirred at the same tempera-

ture for 1 hour. A solid separated, which was washed with anhydrous diethyl ether and recrystallized from ethyl acetate, yield, 16.2 g (87%), mp 125°; uv: λ max nm (log ε) 277 (4.19); ir (chloroform): ν max 1658, 1590 cm^{-1}; nmr (deuteriochloroform): δ 3.15 (s, CH_3N), 3.35 (s, CH_2-2, CH_2-6), 3.44 (s, CH_3N), 8.14 (near s, =CHN).

Anal. Calcd. for $C_8H_{11}NO_2S$: C, 51.87; H, 5.98; N, 7.56. Found: C, 52.01; H, 5.94; N, 7.43.

5*H*-Thiopyrano[4,3-*d*]isoxazol-4(7*H*)-one (IV).

This compound was prepared according to the literature [2], reflux time, 1 hour, yield, 61%, mp 56° from anhydrous diethyl ether-petroleum ether bp 40-70°; uv: λ max nm (log ε) 235.5 (3.80); ir (chloroform): ν max 1687, 1601, 1483, 1419, 1410 cm^{-1}; nmr (deuteriochloroform): δ 3.44 (s, CH_2-5), 4.02 (s, CH_2-7), 8.60 (s, CH-3).

Anal. Calcd. for $C_6H_5NO_2S$: C, 46.44; H, 3.25; N, 9.03. Found: C, 46.29; H, 3.43; N, 8.82.

3,4,5,6-Tetrahydro-5,5-dihydroxy-3-oxo-2*H*-thiopyrano-4-carbonitrile (VI).

This compound was prepared in 75% yield according to the literature [2], mp 198° dec from ethyl acetate; uv: λ max nm (log ε) 234 (3.80), 269.5 (3.97), 295 sh (3.69); ir (potassium bromide): ν max ~3350 broad, 2235, 1840 broad, 1632 cm^{-1}; nmr (DMSO-d_6): δ 3.50 (s, CH_2-2, CH_2-6), 6.9-7.4 (m, 3 OH; disappears with deuterium oxide).

Anal. Calcd. for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.64; H, 3.99; N, 7.97.

4-Iminoformyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (VII).

The solid obtained by chloroform extraction after reaction of II with formamidine acetate (see footnote [a] in Table III) was purified by chromatography on Florisil (diethyl ether) and recrystallization from ethyl acetate, yield, 55%, mp 118°; uv: λ max nm (log ε) 250 (4.00), 292.5 (4.12); ir (chloroform): ν max 3480, 3300 broad, 1667, 1603, 1471, 1408 cm^{-1}; nmr (DMSO-d_6): δ 3.36 (s, CH_2-2, CH_2-6), 7.9-8.4 (m, CH=N), 9.70 (broad m, NH and OH; disappears with deuterium oxide).

Anal. Calcd. for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.62; H, 4.43; N, 8.83.

4-(*t*-Butylhydrazono)formyl-2*H*-thiopyran-3,5(4*H*,6*H*)-dione (VIII).

A solution of II (1.85 g, 10 mmoles) and *t*-butylhydrazine (0.93 g, 10.5 mmoles) in anhydrous ethanol (45 ml) containing acetic acid (1.5 ml) was refluxed for 1 hour. The solvents were evaporated under reduced pressure and the residue was chromatographed on Florisil (diethyl ether). Recrystallization from anhydrous diethyl ether gave the *t*-butylhydrazone VIII as white crystals (0.92 g, 40%), mp 105°; uv: λ max nm (log ε) 256 (3.97), 306 (4.17); ir (chloroform): ν max 1660, 1600 cm^{-1}; nmr (deuteriochloroform): δ 1.12 [s, $(CH_3)_3C$], 3.31 (near s, CH_2-2, CH_2-6), 4.37 (broad s, NH; disappears with deuterium oxide), 8.25 and 8.45 (2 broad s, CH=N), 11.67 (broad s, OH; disappears with deuterium oxide).

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27. Found: C, 52.66; H, 7.14; N, 12.26.

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