Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted α-Aminomethylene Ketones IV. Synthesis of 3,4-Dihydro-5*H*-[1]benzothiopyrano[3,4-*e*]-1,2-oxathiin and 2,3,6,7-Tetrahydro-5*H*-thiopyrano[3,4-*e*]-1,2-oxathiin Derivatives

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The reaction of sulfene with *N,N*-disubstituted 3-aminomethylene-2,3-dihydro-4-thiochromanones and -2,3,5,6-tetrahydro-4-thiopyranones gave 1,4-cycloadducts which are derivatives of new heterocyclic systems, namely 3,4-dihydro-5*H*-[1]benzothiopyrano[3,4-*e*]-1,2-oxathiin and 3,4,7,8-tetrahydro-5*H*-thiopyrano[3,4-*e*]-1,2-oxathiin, respectively. Furthermore, some pyrazole derivatives VII and VIII were prepared from 3-hydroxymethylene-2,3-dihydro-4-thiochromanone or 2,3,5,6-tetrahydro-4-thiopyranone and hydrazines.

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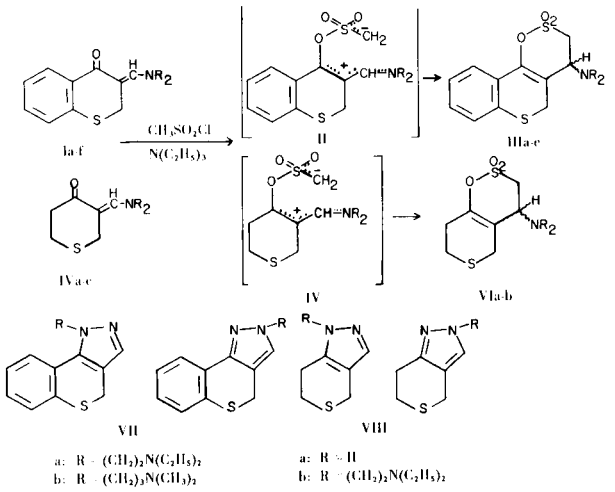
As part of a continuing study of the 1,4-cycloaddition of *N,N*-disubstituted α-aminomethylene ketones to sulfene (1,3), we wish to report the synthesis of new polycondensed sulfur heterocycles, namely, 3,4-dihydro-5*H*-[1]benzothiopyrano[3,4-*e*]-1,2-oxathiin and 3,4,7,8-tetrahydro-5*H*-thiopyrano[3,4-*e*]-1,2-oxathiin.

For this purpose we prepared a series of *N,N*-disubstituted 3-aminomethylene-2,3-dihydro-4-thiochromanones (Ia-f) and 1,2,5,6-tetrahydro-4-thiopyranones (IVa-c) (Tables I, II, III), starting from secondary amines and 3-hydroxymethylene-2,3-dihydro-4-thiochromanone (4) or -2,3,5,6-tetrahydro-4-thiopyranone, respectively. Enamines I and IV are probably E-isomers, at least as can be seen from the strong upfield shift of SCH_2 protons (0.5-0.8 ppm) caused by the phenyl group in compounds Ie-f, IVc (see Table III). *N,N*-Disubstituted 4-amino-3,4-dihydro-5*H*-[1]benzothiopyrano[3,4-*e*]-1,2-oxathiin 2,2-dioxides (IIIa-c) and 4-amino-3,4,7,8-tetrahydro-5*H*-thiopyrano-[3,4-*e*]-1,2-oxathiin 2,2-dioxides (VIa-b) (Table IV) were subsequently obtained in high to fair yield by reacting methanesulfonyl chloride and triethylamine (*in situ* prepared sulfene) with I and IV.



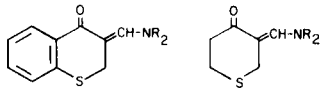
The ir spectra of III and VI (Table V) show the strong SO_2 stretching vibrations at 1352-1383, 1175-1187 cm^{-1}; the olefin band is found at 1647-1663 cm^{-1} in the case of III and at 1681-1685 cm^{-1} in the case of VI, in agreement with our previous findings (1,3). The structure of III is also recognized through the ABX (IIIa,c,e) and AB_2 (IIIb,d) systems of SO_2CH_2CHN protons that are found in the nmr spectra (compare Table VI and references (1,3)). On the other hand the superimposition of the signals in the nmr spectra of VI does not allow a careful analysis.

Cycloaddition occurred with I also when NR_2 was a bulky group like diisopropylamino; a low basicity of the enamines (If, IVc) prevented the reaction or in the case of Ie gave a low yield of the cycloadduct. Thus our previous results on the cycloaddition mechanism were confirmed, and the structures II and IV of the dipolar intermediate appear to be the most likely structures.

Some pyrazole derivatives were prepared for pharma-

Table I

N,N-Disubstituted 3-Aminomethylene-2,3-dihydro-4-thiochromanones (Ia-f) and 3-Aminomethylene-2,3,5,6-tetrahydro-4-thiopyranones (IVa-c)



I IV

Compound	NR_2	Yield %	M.p., °C or B.p., °C/mm Hg	Molecular Formula	Analyses % Calcd./Found C	H	N
Ia	$-N(C_2H_5)_2$	96	105 (a)	$C_{14}H_{17}NOS$	67.98	6.93	5.66
					67.70	6.94	5.81
Ib	$-N[CH(CH_3)_2]_2$	91	152-153 (b)	$C_{16}H_{21}NOS$	69.78	7.69	5.09
					69.98	7.69	5.11
Ic		91	138-139 (b)	$C_{14}H_{15}NOS$	68.54	6.16	5.71
					68.75	6.38	5.85
Id		84	116 (b)	$C_{15}H_{17}NOS$	69.46	6.61	5.40
					69.30	6.36	5.36
Ie	$-N(CH_3)C_6H_5$	74	91 (b)	$C_{17}H_{15}NOS$	72.57	5.37	4.98
					72.30	5.58	5.00
If	$-N(C_6H_5)_2$	80	150 (b)	$C_{22}H_{17}NOS$	76.94	4.99	4.08
					77.18	4.99	4.38
IVa	$-N(C_2H_5)_2$	82	130-135/0.25	$C_{10}H_{17}NOS$	60.26	8.60	7.03
					60.06	8.55	6.98
IVb		83	68 (a)	$C_{11}H_{17}NOS$	62.52	8.11	6.63
					62.38	7.74	6.61
IVc	$-N(CH_3)C_6H_5$	68	87 (a)	$C_{13}H_{15}NOS$	66.92	6.48	6.00
					67.05	6.35	5.90

(a) From diethyl ether. (b) From ethyl acetate.

Table II

Uv and Ir Spectral Data of Compounds I and IV

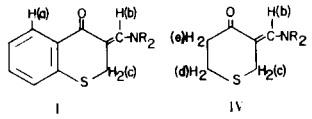
Compound	Uv λ max nm (log ε)	Ir (cm^{-1}) C=O	C=C
Ia	248 (4.30), 260sh (4.15), 368 (4.06)	1635	1530
Ib	247 (4.29), 260sh (4.18), 380 (4.16)	1632	1510
Ic	248.5 (4.28), 260sh (4.19), 376 (4.16)	1638	1512
Id	247 (4.28), 260sh (4.12), 375 (4.02)	1630	1527
Ie	247.5 (4.39), 265sh (4.13), 382 (4.27)	1632	1520
If	248 (4.34), 265 (4.29), 392 (4.27)	1642	1525
IVa	275sh (3.54), 329.5 (4.19)	1638	1540 (a)
IVb	275sh (3.57), 333.5 (4.21)	1628	1525
IVc	230sh (3.77), 342.5 (4.17)	1648	1545

(a) Neat.

cological screening. As was expected, the reaction of 3-hydroxymethylene-2,3-dihydro-4-thiochromanone or -2,3,5,6-tetrahydro-4-thiopyranone with *N*-substituted hydrazines gave a mixture of pyrazoles VII and VIIIb. This was established by nmr spectral data in which a broadening of the pyrazole =CH signal (δ 7.10-7.13), a splitting of the N-N-CH_2 triplet (δ 3.9-4.4) and in the case of VII, a further splitting of the SCH_2 signal (δ 3.76-3.88)

Table III

Nmr Spectral Data of Compounds I and IV



I IV

Chemical Shifts (δ)

Compound	H (a)	Other aromatic protons	H (b)	H (c)	H (d) + H (e)	NR_2
Ia (a)	8.06 (m)	7.23 (m)	7.63 (near s)	3.92 (near s)		1.26 (t, J = 7.3, $2CH_3$) 3.37 (q, J = 7.3, $2NCH_2$)
Ib (a)	8.05 (m)	7.24 (m)	7.84 (near s)	3.93 (near s)		1.30 (d, J = 6.8, $4CH_3$) 3.85 (m, 2CH)
Ic (a)	8.03 (m)	7.19 (m)	7.73 (near s)	3.99 (near s)		1.88 (m, $2CH_2$) 3.55 (m, $2NCH_2$)
Id (a)	8.07 (m)	7.29 (m)	7.64 (near s)	3.88 (near s)		1.62 (m, $3CH_2$) 3.39 (m, $2NCH_2$)
Ie (a)	8.10 (m)	7.26 (m)	7.76 (near s)	3.31 (near s)		3.51 (s, NCH_3) 7.26 (m, C_6H_5)
If (a)	8.10 (m)	7.22 (m)	7.89 (near s)	3.13 (near s)		7.22 (m, $2C_6H_5$)
IVa (b)			7.27 (near s)	3.61 (near s)	2.72 (m)	1.27 (t, J = 7.3, $2CH_3$) 3.37 (q, J = 7.3, $2NCH_2$)
IVb (b)			7.19 (near s)	3.59 (near s)	2.67 (m)	1.66 (m, $3CH_2$) 3.41 (m, $2NCH_2$)
IVc (a)			7.61 (near s)	3.07 (near s)	2.81 (m)	3.46 (s, NCH_3) 7.23 (m, C_6H_5)

(a) In deuteriochloroform. (b) In carbon tetrachloride.

were observed. The ratio of the isomers was 62/38 (VIIa), 70/30 (VIIb) and 50/50 (VIIIb). Also the uv data agree quite well with the pyrazole structure (5,6). Indeed VIIIa showed an absorption maximum at 222 nm; the *N*-alkylation to give VIIIb causes a typical bathochromic shift (+7.5 nm) with a slight hyperchromic effect. Compounds VII behave like phenyl-3(5)pyrazoles, showing the strongest maximum at about 254 nm due to electronic transitions between the aromatic rings.

In conclusion, this new example of 1,4-cycloaddition of heterocyclic enamines to sulfene seems to be a convenient route to the synthesis of 3,4-dihydro-5*H*-[1]benzothiopyrano-[3,4-*e*]-1,2-oxathiin and 3,4,7,8-tetrahydro-5*H*-thiopyrano-[3,4-*e*]-1,2-oxathiin ring systems. Starting from α-hydroxymethylene ketones and hydrazines, the synthesis of the tetrahydrothiopyrano[4,3-*c*]pyrazole and the dihydro-[1]benzothiopyrano[4,3-*c*]pyrazole ring systems was also achieved.

EXPERIMENTAL

Uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. Ir spectra were taken on a Perkin-Elmer Model 257 spectrophotometer in potassium bromide pellets unless otherwise stated. Nmr spectra were recorded on a Perkin Elmer Model R12 instrument (60 Mc/s). Chemical shifts are reported as δ (ppm) relative to TMS as an internal standard; J in Hz. Melting points were determined with a Mettler FP1 apparatus and are uncorrected.

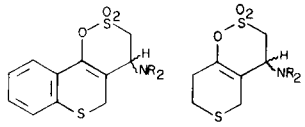
Compounds Ia,c,d, IVa-c were prepared according to (1) and Ib,e,f according to (7). Compounds IIIa-e, VIa-b were prepared by a previously described procedure (1). Anhydrous solvents for the reaction were diethyl ether (IIIa,e, VIa-b) and tetrahydrofuran (IIIb,c,d).

3-Hydroxymethylene-2,3,5,6-tetrahydro-4-thiopyranone.

To a stirred suspension of sodium methoxide (5.4 g., 0.1 mole) in anhydrous benzene (50 ml.) was added a solution of ethyl formate (7.4 g., 0.1 mole) in benzene (20 ml.). To the ice-cooled mixture was added dropwise a solution of 4-tetrahydrothiopyranone (8) (5.8 g., 50 mmoles) in benzene (30 ml.). After stirring for

Table IV

N,N-Disubstituted 4-Amino-3,4-dihydro-5*H*-[1]benzothiopyrano[3,4-*e*]-1,2-oxathiin 2,2-Dioxides (III) and 4-Amino-3,4,7,8-tetrahydro-5*H*-thiopyrano[3,4-*e*]-1,2-oxathiin 2,2-Dioxides (VI)



III VI

Compound	NR_2	Yield %	M.p., °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(C_2H_5)_2$	44	136 (a)	$C_{15}H_{19}NO_3S_2$	55.36	5.88	4.30
					55.46	5.81	4.27
IIIb	$N[CH(CH_3)_2]_2$	64	179-180 (a)	$C_{17}H_{23}NO_3S_2$	57.76	6.56	3.96
					58.00	6.60	3.74
IIIc		64	128-129 (b)	$C_{15}H_{17}NO_3S_2$	55.70	5.30	4.33
					55.50	5.32	4.47
IIId		80	185 (a)	$C_{16}H_{19}NO_3S_2$	56.95	5.67	4.15
					56.78	5.61	4.04
IIIe	$N(CH_3)C_6H_5$	30	154-155 (a)	$C_{18}H_{17}NO_3S_2$	60.14	4.77	3.90
					59.88	5.02	3.87
VIa	$N(C_2H_5)_2$	44	103-104 (c)	$C_{11}H_{19}NO_3S_2$	47.63	6.90	5.05
					48.00	6.68	5.23
VIb		30	123-124 (c)	$C_{12}H_{19}NO_3S_2$	49.80	6.62	4.84
					50.09	6.73	5.06

(a) From ethanol. (b) From methanol. (c) From ether after chromatography on Florisil ®.

Table V

Uv and Ir Spectral Data of Compounds III and VI

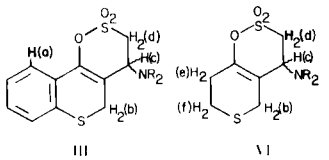
Compound	Uv λ max nm (log ε)	Ir (cm^{-1}) C=C	O=S=O	
IIIa	220 (4.09), 247.5 (4.27), 285 (3.52), 295sh (3.39), 332 (3.22)	1647	1368	1183
IIIb	217 (4.11), 248.5 (4.29), 287 (3.66), 297sh (3.61), 332 (3.52)	1648	1357	1182
IIIc	220 (4.06), 247.5 (4.28), 285 (3.49), 295sh (3.35), 332 (3.20)	1663	1362	1186
IIId	220 (4.09), 248 (4.29), 285 (3.54), 295sh (3.41), 332 (3.26)	1647	1378	1187
IIIe	251.5 (4.59), 287 (3.79), 295sh (3.75), 330 (3.43)	1654	1367	1177
VIa		1685	1383	1187 (a)
VIb		1681	1352	1175

(a) In carbon tetrachloride.

12 hours at room temperature, the precipitate was hydrolyzed with water (50 ml.). The organic layer was extracted with 10% sodium hydroxide and with water. The aqueous portions were combined, washed with ether and acidified with 10% hydrochloric acid with cooling. The oil which separated was extracted with ether, the combined extracts were washed with water, dried over magnesium sulfate and evaporated. Vacuum distillation of the residue gave a light yellow oil, b.p. 80-85° (0.5 mm), yield 3.6 g. (50%); uv λ max nm (log ε): 280 (3.71); ir (carbon tetrachloride) ν max: 1712, 1643, 1585 cm^{-1}; nmr (carbon tetrachloride): δ 2.74 (centered) (m, 4H, SCH_2CH_2), 3.37 (near s, 2H, $SCH_2C=$), 8.48 (s, 1H, =CH), 13.3-14.7 (deuterium oxide-exchangeable broad s,

Table VI

Nmr Spectral Data of Compounds III and VI



III VI

Chemical Shifts (δ)

Compound	H(a)	Other aromatic protons	H(b)	H(c)	H(d)	H(e) + H(f)	NR_2
IIIa (a)	7.48 (m)	7.17 (m)	3.68 (near s)	4.16 (near q) J_{AX} = 4.3 J_{BX} = 13.1	3.30; 3.52 (dq) J_{AB} = 13.2		1.11 (t, J = 7, $2CH_3$) 2.27 (q, J = 7, NCH_2) 2.68 (q, J = 7, NCH_2) (c)
IIIb (a)	7.57 (m)	7.26 (m)	3.66 (near s)	4.12 (near t) J ~ 13	3.55 (m) J ~ 13		1.13 (d, J = 6.6, $4CH_3$) 3.30 (h, J = 6.6, 2NCH)
IIIc (a)	7.50 (m)	7.20 (m)	3.68 (near s)	4.33 (near q) J_{AX} = 6.4 J_{BX} = 11	3.40; 3.60 (dq) J_{AB} = 13.2		1.81 (m, $2CH_2$) 2.72 (m, $2NCH_2$)
IIId (a)	7.53 (m)	7.20 (m)	3.70 (near s)	4.02 (near q) J ~ 10	3.48 (m) J ~ 10		1.54 (m, $3CH_2$) 2.56 (m, $2NCH_2$)
IIIe (a)	7.57 (m)	7.25 (m)	3.60 (near s)	5.17 (near t) J_{AX} = 7.6 J_{BX} = 8.6	3.46; 3.61 (dq) J_{AB} = 13.2		2.96 (s, NCH_3) 6.92 (m, NC_6H_5)
VIa (b)			3.29 (m)	3.96 (m)	3.22; 3.37 (m) J_{AB} = 13.2	2.50 (m)	1.10 (t, J = 7, $2CH_3$) 2.22 and 2.50 (m, $2NCH_2$)
VIb (b)			3.32 (m)	3.76 (m)	3.32 (m)	2.76 (m)	1.53 (m, $3CH_2$) 2.49 (m, $2NCH_2$)

(a) In deuteriochloroform. (b) In carbon tetrachloride. (c) Splitting of the NCH_2 signal.

1H, OH).

Anal. Calcd. for $C_6H_8O_2S$: C, 49.98; H, 5.59. Found: C, 50.07; H, 5.61.

General Procedure for Condensed Pyrazoles VIIa,b, VIIIb.

The α-hydroxymethylene ketone (20 mmoles) and *N*-substituted hydrazine (23 mmoles) were mixed at room temperature and heated at 130° for 2.5 hours. After cooling, the reaction mixture was extracted with ether and the extracts were dried over magnesium sulfate and evaporated. Vacuum distillation of the residue gave a yellow oil.

Compound VIIa.

This compound was obtained in a yield of 82%, b.p. 160-165° (0.2 mm); uv λ max nm (log ε): 225 (4.09), 245 sh (4.20), 254 (4.25), 280 sh (3.83), 318 (3.53); ir (neat) ν max: 1640, 1591, 1570, 1497 cm^{-1}; nmr (carbon tetrachloride): δ 0.97 (t, 6H, J ~ 7, $2CH_3$), 2.52 (q, 4H, J ~ 7, 2 NCH_2), 2.85 (m, 2H, CH_2NR_2), 3.76 and 3.86 (2 near s, 2H, SCH_2), 4.05 and 4.35 (2t, J ~ 6.7, 2H, N-N-CH_2), 7.13 (near s, 1H, =CH), 7.21 (m, $3H_{ar}$), 7.75 (m, $1H_{ar}$).

Anal. Calcd. for $C_{16}H_{21}N_3S$: C, 66.86; H, 7.36; N, 14.62. Found: C, 67.13; H, 7.56; N, 14.42.

Compound VIIb.

This compound was obtained in a yield of 83%, b.p. 170-175° (0.5 mm); uv λ max nm (log ε): 225 (4.07), 245 sh (4.19), 253.5 (4.24), 280 sh (3.80), 318 (3.49); ir (neat) ν max: 1638, 1590, 1570, 1496 cm^{-1}: nmr (carbon tetrachloride): δ 2.17 (s, 6H, $2NCH_3$), 1.8-2.5 (broad m, 4H, $CH_2CH_2NR_2$), 3.78 and 3.88 (2 near s, 2H, SCH_2), 4.12 and 4.39 (2t, J ~ 6.7, 2H, N-N-CH_2), 7.13 (m, 1H, =CH), 7.26 (m, $3H_{ar}$), 7.70 (broad m, $1H_{ar}$).

Anal. Calcd. for $C_{15}H_{19}N_3S$: C, 65.90; H, 7.00; N, 15.37. Found: C, 65.92; H, 7.25; N, 15.56.

Compound VIIIb.

This compound was obtained in a yield of 75% after chromatography on Florisil ®(ether); b.p. 125° (0.35 mm); uv λ max nm (log ε): 229.5 (3.69); ir (neat) ν max: 1640, 1570, 1550, 1482 cm^{-1}; nmr (carbon tetrachloride): δ 0.94 and 0.96 (2t, J ~ 7, 6H, $2CH_3$), 2.57 (m, 6H, $3NCH_2$), 2.81 (near s, 4H, SCH_2-CH_2), 3.52 (near s, 2H, SCH_2C=), 3.88 and 3.93 (2t, J ~ 7, 2H, N-N-CH_2), 7.10 (near s, 1H, =CH).

Anal. Calcd. for $C_{12}H_{21}N_3S$: C, 60.21; H, 8.84; N, 17.55. Found: C, 60.05; H, 8.74; N, 17.65.

1,5,7,8-(or 2,5,7,8)Tetrahydrothiopyrano[4,3-*c*]pyrazole (VIIIa).

A solution of 3-hydroxymethylene-2,3,5,6-tetrahydro-4-thiopyranone (2 g., 14 mmoles) and 100% hydrazine hydrate (1.30 g., 26 mmoles) in 50 ml. of ethanol was refluxed for 2 hours. The ethanol was removed under reduced pressure and the residue taken up in dichloromethane and chromatographed on Florisil ®, yield 1.4 g. (71%); m.p. 116.5° from ether; uv λ max nm (log ε): 222 (3.56); ir (carbon tetrachloride) ν max: 3465, 3145, 1593, 1505, 1475 cm^{-1}; nmr (carbon tetrachloride): δ 2.91 (m, 4H, SCH_2CH_2), 3.64 (near s, 2H, SCH_2C=), 7.23 (near s, 1H, =CH), 12.31 (centered) (deuterium oxide-exchangeable m, 1H, NH).

Anal. Calcd. for $C_6H_8N_2S$: C, 51.40; H, 5.75; N, 19.98. Found: C, 51.24; H, 5.47; N, 19.86.

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