Reactions of 1,3-Thiazine-2,6-dithiones. Part 5 [1]. Novel Synthesis of 3,5-Dicyano-4-thiopyridones *via* 2-Cyanomethyldihydro-1,3-thiazine-6-thiones

Motomu Muraoka* and Tatsuo Yamamoto

Department of Chemistry, Faculty of Science, Josai University,
Keyaki-Dai, Sakado, Saitama 350-02, Japan

Received February 23, 1984

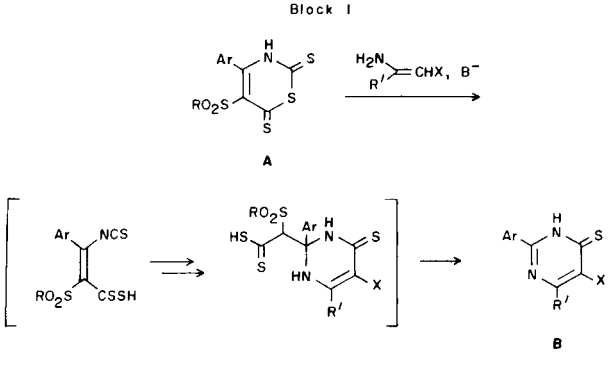
A novel synthesis of a series of 2,6-disubstituted 3,5-dicyano-4-thiopyridones **4** by the decomposition of 2,4-disubstituted 5-cyano-2-cyanomethyldihydro-1,3-thiazine-6-thiones **2**, which are synthesized from 4-substituted 5-cyano-1,3-thiazine-2,6-dithiones and enaminonitriles, is described.

J. Heterocyclic Chem., **21**, 1445 (1984).

We have previously reported the reactions of 1,3-thiazine-2,6-dithiones with 1,ω-diamines, 1,2-phenylenediamine, and semicarbazide to give nitrogen containing condensed hetero ring compounds [2,3]. There are several reports concerning the synthesis of condensed hetero ring compounds using trithioisatoic anhydride by Leistner and his co-workers [4-7], who obtained several types of the compounds from the reaction with 1,ω-diamines, 1,ω-aminoalcohols, ω-aminoaldehydedimethylacetal, and aminoguanidine together with quinazoline-2,4-dithiones [8].

In our recent study, we reported that 1,3-thiazine-2,6-dithiones **A** bearing an alkyl- or an arylsulfonyl group at position 5, react with both enaminonitriles and -sulfones in the presence of a base in tetrahydrofuran to produce a series of pyrimidine-4(3*H*)-thiones **B** as a sole product [9]. The pyrimidinethiones **B** have been considered to be formed *via* several transient intermediates as shown below.

Block 1



5-Cyano-1,3-thiazine-2,6-dithiones, however, did not react with the carbanions of the enaminonitriles under the same reaction conditions as those mentioned above in tetrahydrofuran except for one case.

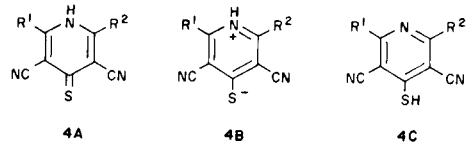
In contrast, we now find that the 5-cyanothiazinedithiones, when the reaction is carried out in a polar aprotic solvent such as dimethylformamide at 80°, take another reaction course towards enaminonitriles to afford 2,4-disubstituted 2-cyanomethyl-2,3-dihydro-1,3-thiazine-6(6*H*)-thiones **2a-l**.

We wish to describe a novel synthesis of 3,5-dicyano-4-thiopyridones **4a-i** by the decomposition of the 2-cyanomethyl-1,3-thiazine-6-thiones **2a-l**. Thus, compounds **2a-l** were obtained when 4-aryl-5-cyano-1,3-thiazine-2,6-dithiones were treated with enaminonitriles in dimethylformamide at 80° in the presence of 2 molar equivalents of sodium 1,1-dimethylpropanolate in moderate yields (Table 1).

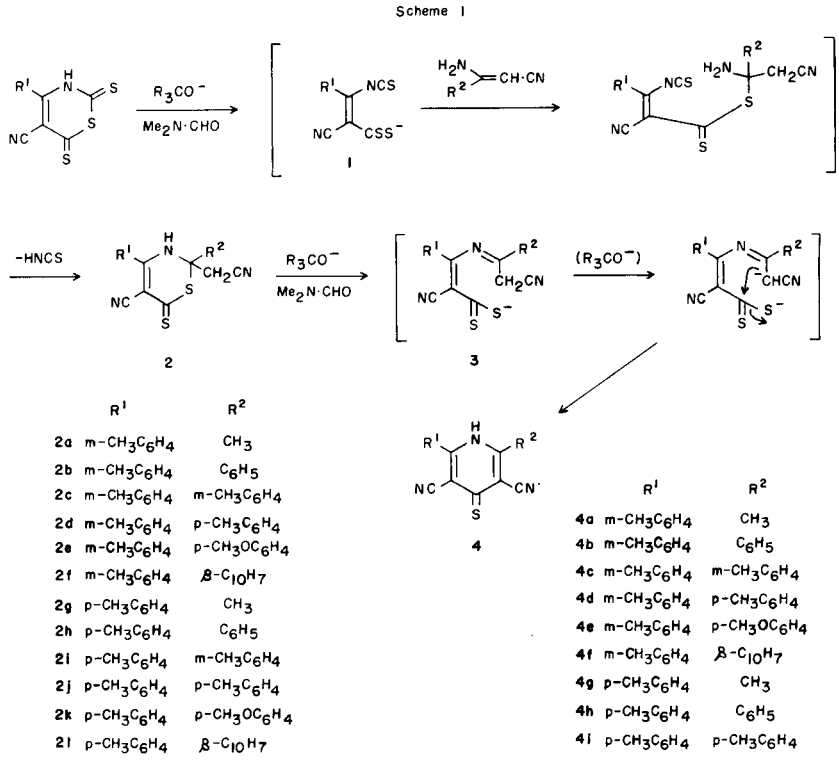
Furthermore, we find that those 2-cyanomethylthiazinethiones **2a-j**, when refluxed again with 2 molar equivalents of the base in dimethylformamide at 90°, afforded 3,5-dicyano-4-thiopyridones **4a-i** in very excellent yield in most cases. Use of equal molar equivalents of the base failed to give rise to conversion of compounds **2a-j** into the 4-thiopyridones **4a-i**. The fact that each thiopyridone produced from compound **2d** and **2i** is identical to the other (mp and ir) also strongly supports **4a-i** to be of 4-thiopyridone structure (Table 3).

This method of preparation of 4-thiopyridones is of a novel type and 3,5-dicyano-4-thiopyridones were first synthesized by this method. One of the best known preparative methods of 4-thiopyridones which bear no substituent on the imino nitrogen atom is the one through substitution of halogen in 4-halopyridines by a mercapto group [10]. The preparative methods by the reaction of 4-hydroxypyridines with phosphorus pentasulfide [11] and of *N*-pyridyl-4-pyridinium chlorides with hydrogen sulfide [12] have also been reported. In comparison with those of simple 4-thiopyridones [13,14], ir and uv visible spectra of the 4-thiopyridones here obtained support that compounds **4a-i** exist rather as neutral thione form **4A** or zwitterion form **4B** than as 4-mercaptopyridine **4C**.

Block 2



Scheme I

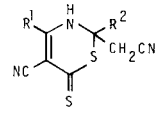


	R¹	R²
2a	m-$CH_3C_6H_4$	CH_3
2b	m-$CH_3C_6H_4$	C_6H_5
2c	m-$CH_3C_6H_4$	m-$CH_3C_6H_4$
2d	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$
2e	m-$CH_3C_6H_4$	p-$CH_3OC_6H_4$
2f	m-$CH_3C_6H_4$	β-$C_{10}H_7$
2g	p-$CH_3C_6H_4$	CH_3
2h	p-$CH_3C_6H_4$	C_6H_5
2i	p-$CH_3C_6H_4$	m-$CH_3C_6H_4$
2j	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$
2k	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$
2l	p-$CH_3C_6H_4$	β-$C_{10}H_7$

	R¹	R²
4a	m-$CH_3C_6H_4$	CH_3
4b	m-$CH_3C_6H_4$	C_6H_5
4c	m-$CH_3C_6H_4$	m-$CH_3C_6H_4$
4d	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$
4e	m-$CH_3C_6H_4$	p-$CH_3OC_6H_4$
4f	m-$CH_3C_6H_4$	β-$C_{10}H_7$
4g	p-$CH_3C_6H_4$	CH_3
4h	p-$CH_3C_6H_4$	C_6H_5
4i	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$

Table 1

2,4-Disubstituted 5-Cyano-2-cyanomethyl-2,3-dihydro-1,3-thiazine-6(6*H*)-thiones **2a-l**

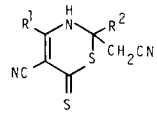


Compound	R¹	R²	Mp, °C [a]	Yield (%)	Molecular Formula	Analyses % Calcd./Found C	H	N	S
2a	m-$CH_3C_6H_4$	CH_3	248-249	67	$C_{15}H_{13}N_3S_2$	60.17	4.38	14.03	21.41
						60.17	4.42	13.66	21.46
2b	m-$CH_3C_6H_4$	C_6H_5	230-232	34	$C_{20}H_{15}N_3S_2$	66.44	4.18	11.63	17.74
						66.34	4.27	11.92	17.91
2c	m-$CH_3C_6H_4$	m-$CH_3C_6H_4$	140-141	86	$C_{21}H_{17}N_3S_2$	67.17	4.57	11.20	17.07
						67.07	4.52	10.71	16.92
2d	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$	240-241	65	$C_{21}H_{17}N_3S_2$	67.17	4.57	11.20	17.07
						66.91	4.49	10.81	16.81
2e	m-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	235-236	69	$C_{21}H_{17}N_3SO_2$	64.42	4.38	10.74	16.38
						64.07	4.45	10.57	16.48
2f	m-$CH_3C_6H_4$	β-$C_{10}H_7$	229	76	$C_{24}H_{17}N_3S_2$	70.04	4.17	10.21	15.58
						70.09	4.16	10.29	15.87
2g	p-$CH_3C_6H_4$	CH_3	244-245	56	$C_{15}H_{13}N_3S_2$	60.17	4.38	14.03	21.41
						60.41	4.44	13.77	21.54
2h	p-$CH_3C_6H_4$	C_6H_5	234-235	40	$C_{20}H_{15}N_3S_2$	66.44	4.18	11.63	17.74
						66.15	4.12	11.46	17.89
2i	p-$CH_3C_6H_4$	m-$CH_3C_6H_4$	240-241	31	$C_{21}H_{17}N_3S_2$	67.17	4.57	11.20	17.07
						67.46	4.67	11.34	17.39
2j	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	229-230	44	$C_{21}H_{17}N_3S_2$	67.17	4.57	11.20	17.07
						67.23	4.68	10.91	17.29
2k	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	226	56	$C_{21}H_{17}N_3OS_2$	64.42	4.38	10.74	16.38
						64.14	4.37	10.54	16.63
2l	p-$CH_3C_6H_4$	β-$C_{10}H_7$	233-234	54	$C_{24}H_{17}N_3S_2$	70.04	4.17	10.21	15.58
						69.70	4.12	10.24	15.77

[a] Compounds **2a-l** were recrystallized from aqueous acetone.

Table 2

Spectral Properties of Compounds **2a-l**



Compound	IR (Potassium bromide), cm^{-1}	UV and Visible (Ethanol) λ max (log ε), nm	^1H NMR (Pyridine-d_5) (δ, ppm)
2a	3250, 2232, 1503, 1359, 1250	267 (3.96), 324 (3.57), 389 (4.23)	7.15-8.09 (m, 4H), 7.75 (br) (s, 1H), 4.00 (d, 1H, J = 17), 3.55 (d, 1H, J = 17), 2.08 (s, 3H), 2.03 and 2.06 (each s, 3H in total)
2b	3275, 2225, 1501, 1360, 1270, 1104	263 (4.10), 323 (3.60), 386 (4.09) [a]	7.10-8.14 (m, 9H), 6.10 (br) (s, 1H), 4.34 (d, 1H, J = 17), 4.17 (d, 1H, J = 17), 2.11 (s, 3H)
2c	3345, 3200, 2225, 1501, 1359, 1271, 1105	263 (4.15), 324 (3.63), 386 (4.09)	7.15-8.00 (m, 8H), 6.55 (br) (s, 1H), 4.40 (d, 1H, J = 17), 4.21 (d, 1H, J = 17), 2.01, 2.04 and 2.07 (each s, 6H in total)
2d	3240, 2220, 1500, 1360, 1271, 1103	265 (4.08), 327 (3.65), 390 (4.21)	7.92 (d, 2H), 7.25-7.90 (m, 4H), 7.18 (d, 2H), 6.30 (br) (s, 1H), 4.33 (d, 1H, J = 16), 4.18 (d, 1H, J = 16), 2.02, 2.11 and 2.16 (each s, 6H in total)
2e	3200, 2224, 1490, 1356, 1259, 1100	266 (4.09), 326 (3.63), 390 (4.18)	8.50 (br) (s, 1H), 7.98 (d, 2H), 7.10-7.90 (m, 4H), 6.97 (d, 2H), 4.35 (d, 1H, J = 17), 4.22 (d, 1H, J = 17), 3.62 (s, 3H), 2.02 and 2.10 (each s, 3H in total)
2f	3180, 2224, 1491, 1358, 1257, 1099	265 (4.36), 322 (3.75), 388 (4.09)	7.08-8.30 (m, 11H), 6.80 (br) (s, 1H), 4.43 (d, 1H, J = 17), 4.35 (d, 1H, J = 17), 2.00 and 2.11 (each s, 3H in total)
2g	3240, 2225, 1496, 1360, 1239, 1168	273 (4.11), 320 (3.71), 389 (4.26)	7.71 (d, 2H), 7.09 (d, 2H), 5.80 (br) (s, 1H), 3.98 (d, 1H, J = 18), 3.41 (d, 1H, J = 18), 2.07 (s, 3H), 1.99 (s, 3H)
2h	3200, 2220, 1492, 1354, 1245, 1501	269 (4.16), 324 (3.55), 386 (4.11)	7.10-8.16 (m, 9H), 6.95 (br) (s, 1H), 4.40 (d, 1H, J = 17), 4.15 (d, 1H, J = 17), 2.16 (s, 3H)
2i	3195, 2222, 1491, 1358, 1252, 1102	269 (4.17), 324 (3.56), 386 (4.11)	6.98-7.95 (m, 8H), 6.70 (br) (s, 1H), 4.38 (d, 1H, J = 17), 4.18 (d, 1H, J = 17), 1.99, 2.06 and 2.08 (each s, 6H in total)
2j	3195, 2222, 1500, 1360, 1249, 1101	270 (4.16), 324 (3.68), 389 (4.13)	7.85 (d, 4H), 7.08 (d, 4H), 6.60 (br) (s, 1H), 4.34 (d, 1H, J = 17), 4.18 (d, 1H, J = 17), 2.01 and 2.14 (each s, 6H in total)
2k	3200, 2220, 1489, 1352, 1259, 1100	271 (4.18), 324 (3.66), 389 (4.15)	6.90-8.10 (m, 8H), 4.40 (d, 1H, J = 17), 4.21 (d, 1H, J = 17), 3.61 (s, 3H), 2.13 (s, 3H)
2l	3180, 2223, 1493, 1358, 1256, 1099	269 (4.39), 322 (3.65), 388 (4.13)	8.58 (br) (s, 1H), 7.01-8.18 (m, 11H), 4.39 (br) (s, 2H), 2.11 (s, 3H)

[a] In dioxane.

In view of the fact that each 2 molar equivalents of base was required for both effective formation of 2,3-dihydro-1,3-thiazine-6-thiones **2a-l** and complete conversion of these compounds **2** into 4-thiopyridones **4a-i**, it is reasonable to postulate that each step of these reactions proceeds through respective dithiocinnamate type intermediates **1** and **3**, which are similar to that in the formation of 1,3,5-thiadiazine-4-thiones [9]. A suggested mechanism for the formation of compounds **2** and **4** is shown in Scheme 1.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were determined on a Nippon-Bunko A-302 infrared spectrophotometer. The ^1H nmr spectra were recorded on a JEOL-C60HL instrument with TMS as internal standard. The electronic absorption spectra were obtained on a Shimadzu MPS-5000 multi-purpose spectrophotometer.

4-(*m*-tolyl)- and 4-(*p*-tolyl)-5-cyano-1,3-thiazine-2,6(3*H*)-dithiones [15] were prepared by the published literature procedures.

Synthesis of 2-Cyanomethyl-2,3-dihydro-1,3-thiazine-6-thiones (**2a-l**).

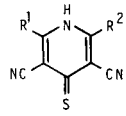
A mixture of 5-cyano-4-aryl-1,3-thiazine-2,6(3*H*)-dithione (2.00 mmoles), each enaminonitrile (2.00 mmoles), sodium 1,1-dimethylpropanolate (4.00 mmoles), and dimethylformamide (15 ml) was refluxed at 80° for 4 hours. Water (50 ml) was added to the cooled reaction mixture and the aqueous solution was washed twice with ether. The aqueous solution from which the remaining ether was removed under reduced pressure, was acidified with 2*M* hydrochloric acid. The resulting red crystals were collected, washed with water, then dissolved in 2% aqueous ammonia. The ammoniacal solution was filtered and acidified again with 2*M* hydrochloric acid to give red crystals of compounds **2**, which were purified by recrystallization from aqueous acetone.

Conversion of 2-Cyanomethyl-2,3-dihydro-1,3-thiazine-6-thiones **2** into 2,6-Disubstituted 3,5-Dicyano-4-thiopyridones **4a-i**.

A solution of 2,4-disubstituted 2-cyanomethyl-2,3-dihydro-1,3-thiazine-6-thione **2** (0.60 mmole) and sodium 1,1-dimethylpropanolate (1.25 mmoles) in dried dimethylformamide (12 ml) was refluxed at 90° for 5 hours. After cooling to room temperature was added water (35 ml) and the aqueous solution was washed twice with ether. The ether remaining in the aqueous solution was removed under reduced pressure. The aqueous solution was acidified with 2*M* hydrochloric acid to separate as a

Table 3

2,6-Disubstituted 3,5-Dicyano-2-thiopyridones **4a-i**

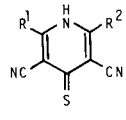


Compound	R^1	R^2	Mp, °C [a]	Yield (%)	Molecular Formula	Analyses % Calcd./Found C	H	N	S
4a	m-$CH_3C_6H_4$	CH_3	242	79	$C_{15}H_{11}N_3S$	67.90	4.18	15.84	12.07
						67.93	4.13	15.90	12.29
4b	m-$CH_3C_6H_4$	C_6H_5	234 [b]	93	$C_{20}H_{13}N_3S$	73.36	4.00	12.86	9.78
						73.59	4.12	13.00	10.02
4c	m-$CH_3C_6H_4$	m-$CH_3C_6H_4$	227-228 [c]	88	$C_{21}H_{15}N_3S$	73.87	4.43	12.31	9.39
						73.59	4.23	12.62	9.59
4d	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$	236	97 [d]	$C_{21}H_{15}N_3S$	73.87	4.43	12.31	9.39
						73.62	4.64	12.28	9.80
4e	m-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	130-139	13 [c]	$C_{21}H_{15}N_3OS$	70.57	4.23	11.76	8.97
						70.24	4.17	11.95	9.24
4f	m-$CH_3C_6H_4$	β-$C_{10}H_7$	186-187	43	$C_{24}H_{15}N_3S$	76.36	4.01	11.14	8.50
						76.32	4.04	11.40	8.63
4g	p-$CH_3C_6H_4$	CH_3	296-297	90	$C_{15}H_{11}N_3S$	67.90	4.18	15.84	12.07
						67.63	4.19	15.83	12.42
4h	p-$CH_3C_6H_4$	C_6H_5	256	88	$C_{20}H_{13}N_3S$	73.36	4.00	12.86	9.78
						73.28	3.95	13.14	9.78
4i	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	257-258	66	$C_{21}H_{15}N_3S$	73.87	4.43	12.31	9.39
						73.56	4.68	12.60	9.71

[a] Compounds **4a-i** were purified by recrystallization from acetic acid. [b] 258-260° on rapid heating. [c] 242-243° on rapid heating. [d] Also obtained from **2i** in 76%.

Table 4

Spectral Properties of Compounds **4a-i** [a]



Compound	IR (Potassium bromide) cm^{-1}	UV and Visible (Ethanol) λ max (log ε), nm
4a	3200, 2845-2520 [b], 1564, 1252, 1206	267 (4.31), 323 (4.28), 370 (3.51)
4b	3200, 2880-2620 [b], 1560, 1260, 1206	268 (4.49), 328 (4.26), 297 (3.30)
4c	3220 (br), 2890-2405 [b], 1564, 1254	269 (4.48), 328 (4.26), 395 (3.39)
4d	3200, 2870-2520 [b], 1588, 1550, 1250, 1076	272 (4.51), 328 (4.26), 393 (3.40)
4e	3120 (br), 2830, 2740, 2545, 1495, 1251, 1180	281 (4.43), 318 (4.44), 376 (3.48)
4f	3310, 1568, 1256, 1069	269 (4.65), 310 (4.40), 323 (4.40), 400 (3.40)
4g	3240 (br), 3180 (br), 1562, 1500	272 (4.28), 282 (4.29), 323 (4.25), 370 (3.43)
4h	3220, 2720-2520 [b], 1592, 1560, 1249, 1078	271 (4.51), 286 (4.43), 327 (4.26), 395 (3.41)
4i	3210, 2870-2680 [b], 1596, 1559, 1262, 1250, 1078	278 (4.50), 323 (4.25), 393 (3.39)

[a] The ^1H nmr spectra for **4a** and **4d** in hexadeuteriodimethylsulfoxide; **4a**: δ 7.64 (m, 4H), 4.39 (br) (s, 1H), 2.53 (s, 3H), 2.41 (s, 3H); **4d**: δ 8.34 (br) (s, 1H), 7.74-7.30 (m, 8H), 2.40 (s, 6H). [b] Several broadened peaks.

yellow solid, which was washed with water, with 2% aqueous ammonia, and again with water. Recrystallization from acetic acid gave pure 4-thiopyridones **4a-i**.

REFERENCES AND NOTES

[1] Paper **4** in this series; T. Yamamoto and M. Muraoka, *J.Chem. Res. (S)*, in press.

[2] T. Yamamoto, M. Muraoka and T. Takeshima, *J. Chem. Res. (S)*, 384 (1979).

[3] T. Yamamoto, M. Muraoka, M. Takahashi and T. Takeshima, *ibid., (S)*, 148 (1980); *(M)*, 2059 (1980).

[4] S. Leistner and G. Wagner, *Z. Chem.*, 289 (1972).

[5] *Idem., Pharmazie*, **35**, 124 (1980).

[6] *Idem., ibid.*, **35**, 582 (1980).

[7] S. Leistner, G. Wagner and Th. Strohscheidt, *ibid.*, **35**, 293 (1980).

[8] S. Leistner, A. P. Giro and G. Wagner, *ibid.*, **33**, 185 (1978).

[9] T. Yamamoto and M. Muraoka, *J. Chem. Res. (S)*, 274 (1982); *(M)*, 2816 (1982).

[10] For example, see E. Koenichs and G. Kinne, *Chem. Ber.*, **54**, 1357 (1921); C. Hansch and W. Carpenter, *J. Org. Chem.*, **22**, 936 (1957).

[11] H. King and L. L. Ware, *J. Chem. Soc.*, 873 (1939).

[12] D. Jerchel, H. Fischer and K. Thomas, *Chem. Ber.*, **89**, 2921 (1956).

[13] E. Spinner, *J. Chem. Soc.*, 1237 (1960).

[14] S. F. Mason, *ibid.*, 219 (1960).

[15] M. Muraoka, T. Yamamoto, S. Yamaguchi, F. Tonosaki, T. Takeshima and N. Fukada, *J. Chem. Soc., Perkin Trans. I*, 1273 (1977).