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Studies on Bi-heterocyclic Compounds. I. 6-Substituted Dihydro-1,4-thiazinones[1)]

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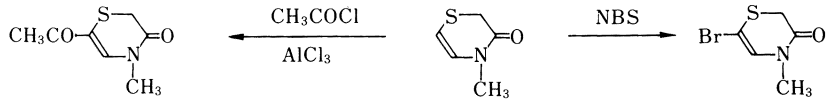
Reactions of 5-methyl-2*H*-1,4-thiazin-3(4*H*)-one (**4**) with various *N*-acylpyridinium salts (**7a**—**g**) led to (*N*-acyldihydropyridyl)thiazinones (**5a**—**g**), oxidation of which yielded a new class of pyridylthiazinones (**6a**—**g**). These reactions were applied to the synthesis of other azaarylthiazinones. Some of these azaarylthiazinones, particularly 6-(4-pyridyl)thiazinones (**6a**, **14a** and **14b**) showed positive inotropic activity with little chronotropic effect on guinea pig left atria.

Keywords——1,4-thiazine; dihydropyridine; dihydropyridyl-1,4-thiazinone; pyridyl-1,4-thiazinone; *N*-acylpyridinium salt; oxidation; positive inotropic activity; congestive heart failure; bi-heterocyclic compound

Some chemical reactions of dihydro-1,4-thiazinones such as **1** are known,[2)] but the number of examples is relatively few. Recently, Hojo *et al.* reported that the *N*-methyl-1,4-thiazinone (**1**) undergoes electrophilic attack at the 6-position; for example, Friedel–Crafts acylation[3)] or bromination[4)] of **1** gave the 6-acetyl (**2**) or 6-bromo derivative (**3**), respectively.



2 **1** **3**

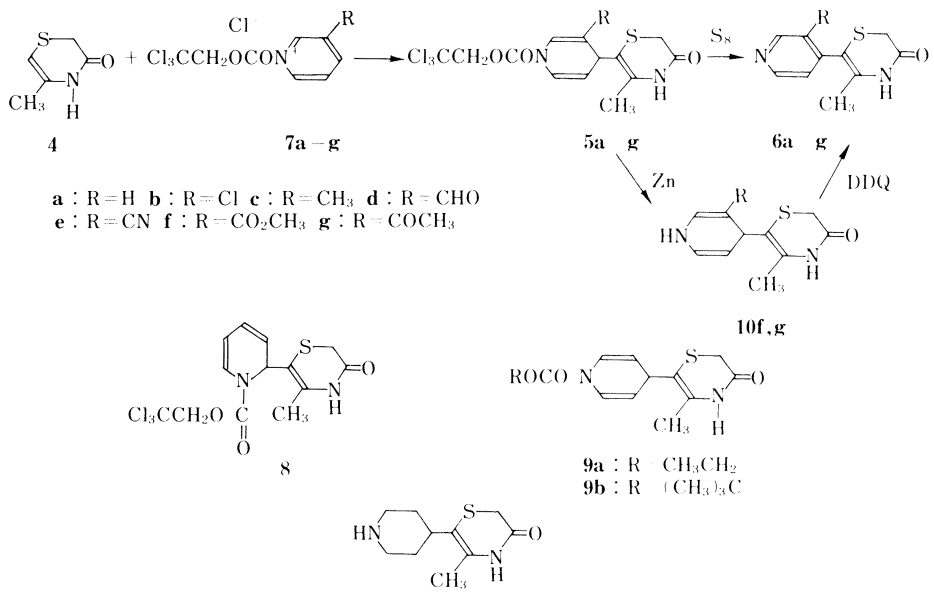
Chart 1

During our extensive synthetic studies on dihydro-1,4-thiazinones, it was found that 5-methyl-2*H*-1,4-thiazin-3(4*H*)-one (**4**) undergoes electrophilic substitution reactions at the 6-position just as well, even though the nitrogen atom is not substituted. We report here the substitution reaction with several *N*-acylpyridinium salts to form the corresponding 6-(1,4-dihydropyridyl)thiazinones (**5a**—**g**), and the oxidative transformation of **5a**—**g** to the 6-pyridylthiazinones (**6a**—**g**). Some of the 6-pyridylthiazinones thus obtained showed a potent positive inotropic activity with little chronotropic effect on guinea pig atria.

5-Methyl-2*H*-1,4-thiazin-3(4*H*)-one (**4**) was prepared by the method of Rao *et al.*[5)] and treated with 2,2,2-trichloroethyl chloroformate in the presence of pyridine in acetonitrile, affording the substituted thiazinone (**5a**) in 81% yield. The infrared (IR) spectrum of **5a** exhibited absorptions at 1720 and 1670 cm^{-1}, indicating the presence of urethane and amide carbonyl moieties, respectively. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5a** showed singlets at δ 1.99 due to the 5-methyl protons and at δ 3.23 due to the 2-methylene protons of the thiazinone skeleton. In addition, disappearance of the signal due to

the 6-proton (6-H) at δ 5.25 in **4** suggests the existence of a 6-substituent in **5a**. Further, doublet at δ 6.97 with a coupling constant (J) of 7 Hz may be ascribed to H-2 and H-6 of an α,β-unsubstituted dihydropyridine ring, reflecting the 4-substituted 1,4-dihydropyridine structure of **5a**. The signals of H-3 and H-5 of the dihydropyridine ring appear as a multiplet at δ 4.80, which overlaps with signals due to the methylene protons of the trichloroethyl group, while the γ-proton signal appears as a multiplet at δ 4.16.

No isomeric 1,2-dihydro-2-pyridyl compound (**8**) was detected in the reaction product, suggesting that this reaction proceeds regioselectively.



a : R=H **b** : R=Cl **c** : R=CH_3 **d** : R=CHO
e : R=CN **f** : R=CO_2CH_3 **g** : R=$COCH_3$

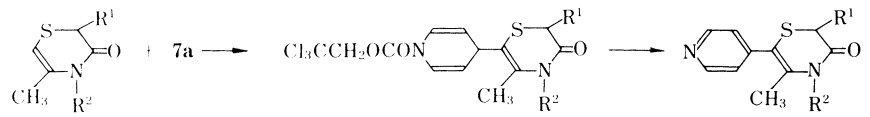
9a : R=CH_3CH_2
9b : R=$(CH_3)_3C$

Chart 2

The 1-ethoxycarbonyl and 1-*tert*-butoxycarbonyl salts were also found to react with **4** to give the corresponding analogs of **5a**, but the yield was not satisfactory.

The dihydropyridine compound (**5a**) was readily oxidized with sulfur at 140 °C to provide the 6-pyridylthiazinone (**6a**) in good yield. The structure of **6a** was assigned on the basis of spectral evidence. The IR spectrum of **6a** lacked the absorption due to the urethane group. The presence of a 4-substituted pyridine ring in **6a** was shown by its NMR signals at δ 7.30 (dd, J=1.5, 5 Hz, H-3 and H-5) and δ 8.60 (d, J=5 Hz, H-2 and H-6).

When using 3-substituted pyridinium salts, including the 3-chloro, 3-methyl, 3-formyl, 3-cyano, 3-methoxycarbonyl and 3-acetyl derivatives (**7b**—**g**), reactions with the thiazinone (**4**) proceeded similarly, giving the corresponding 3-substituted 6-[1-(2,2,2-trichloroethoxycarbonyl)-1,4-dihydro-4-pyridyl]thiazinones (**5b**—**g**). Oxidation of these dihydropyridine derivatives (**5**—**e**) with sulfur provided the corresponding 3-substituted 6-pyridylthiazinones (**6b**—**e**), while the 3-methoxycarbonyl and 3-acetyl derivatives (**5f** and **5g**) gave only a complex tar under the same conditions. Treatment of **5f** and **5g** with zinc powder in aqueous tetrahydrofuran under acidic conditions (pH 4—5) afforded dihydropyridylthiazinones (**10f** and **10g**, respectively). The structures of **10f** and **10g** were confirmed by the appearance of secondary amine absorptions at 3300 cm^{-1} in the IR spectra and the disappearance of the urethane absorption. The dihydropyridine compounds (**10f** and **10g**) were readily oxidized by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in acetonitrile



12a—c 13a—c 14a—c

a : R^1 = CH_3, R^2 = H b : R^1 = CH_3CH_2, R^2 = H c : R^1 = H, R^2 = CH_3

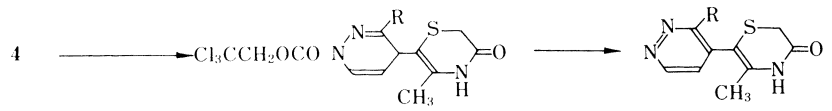
Chart 3

to give 6-pyridylthiazinones (**6f** and **6g**, respectively). On the other hand, treatment of the unsubstituted dihydropyridine (**5a**) with zinc powder in formic acid failed to afford the *N*-deacylated dihydro-compound, but gave 6-(4-piperidyl)thiazinone (**11**) along with a small amount of 6-pyridylthiazinone (**6a**).

2,5-Dimethyl- and 2-ethyl-5-methylthiazinones (**12a** and **12b**) were obtained by the same method as reported for the synthesis of **4**[5] (see Experimental). Treamtent of **12a** and **12b** with the pyridinium salt **7a** followed by oxidation of the resulting 7-dihydropyridylthiazinones (**13a** and **13b**) with sulfur afforded the 2-substituted 4-pyridylthiazinones (**14a** and **14b**, respectively) in good yields. The 4,5-dimethylthiazinone (**12c**), obtained by reaction of **4** with methyl iodide in the presence of sodium hydride,[6] was also treated with **7a** to provide the dihydropyridylthiazinone (**13c**), but in a lower yield. Treatment of **13c** with sulfur gave the pyridylthiazinone (**14c**).

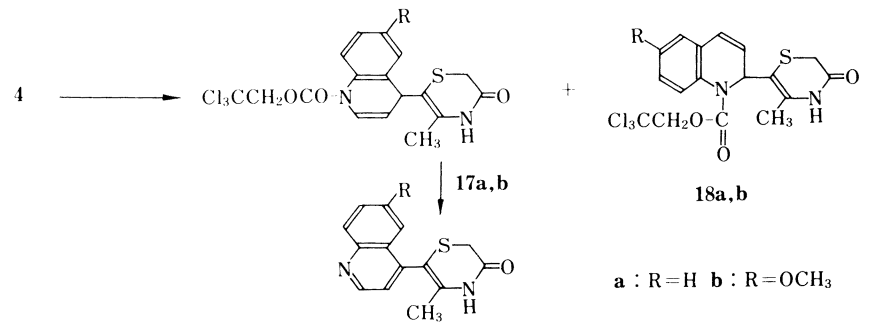
Next, we examined the substitution reactions of the thiazinone (**4**) with salts derived from other heterocycles such as pyridazine, quinoline and thiazole.

Treatment of **4** with pyridazine in the presence of 2,2,2-trichloroethyl chloroformate gave the dihydropyridazinylthiazinone (**15a**), oxidation of which with sulfur provided the 6-pyridazinylthiazinone (**16a**). The NMR spectrum of **16a** exhibited a doublet of doublets at δ 7.65 assignable to H-5 of the pyridazine ring coupled to a doublet at δ 9.20 due to H-6 (J =



15a,b **16a,b**

a : R = H b : R = CH_3



17a,b

18a,b

a : R = H b : R = OCH_3

19a,b

Chart 4

5 Hz) and a doublet at δ 9.25 due to H-3 (J = 2.4 Hz), indicating a presence of a 4-substituted pyridazine ring. Reaction of **4** with a salt derived from 3-methylpyridazine gave **15b**. Oxidation of **15b** yielded the 6-pyridazinylthiazinone (**16b**).

Reaction of **4** with quinoline in the presence of 2,2,2-trichloroethyl chloroformate gave a mixture of (1,4-dihydro-4-quinolyl)thiazinone (**17a**) and (1,2-dihydro-2-quinolyl)thiazinone (**18a**) in a ratio of 4 : 1. The NMR spectrum of **17a** exhibited a spectral pattern similar to those of (1,4-dihydro-4-pyridyl)thiazinones (**5a**—**g**): a doublet at δ 4.62 due to H-4 of the quinoline ring, a doublet of doublets at δ 5.20 due to H-3 and a doublet at δ 7.21 due to H-2 with $J_{2,3}$ of 8 Hz and $J_{3,4}$ of 4 Hz, suggesting a 4-substituted 1,4-dihydroquinoline structure for **17a**. Further, oxidation of **17a** gave 4-quinolylthiazinone (**19a**), whose NMR spectrum showed a doublet at δ 7.35 due to H-3 and a doublet at δ 8.95 due to H-2 with $J_{2,3}$ of 4.4 Hz, confirming the existence of the 4-substituted quinoline structure for **19a**. The NMR spectrum of the isomeric dihydroquinolylthiazinone (**18a**) differed from that of **17a**, exhibiting a marked upfield shift of a doublet at δ 6.13 with J of 6 Hz in comparison with that (δ 4.62) in **17a**. Considering the electronic effects of the neighboring nitrogen atom, the doublet at δ 6.13 may be assignable to H-2, suggesting the 2-substituted 1,2-dihydroquinoline structure for **18a**. Oxidation of **18a** with sulfur gave a complex tar, from which the desired quinoline product could not be obtained.

Reaction of the thiazinone (**4**) with a 6-methoxyquinolinium salt proceeded analogously to give the 4-substituted compound (**17b**) and the 2-substituted compound (**18b**) in a ratio of 1 : 1. Oxidation of **17b** with sulfur gave the 6-(4-quinolyl)thiazinone (**19b**).

Some electrophilic properties of thiazolium salts are well knwon.[7] Similar reactions of the thiazinone (**4**) with thiazole in the presence of ethyl chloroformate or 2,2,2-trichloroethyl chloroformate were carried out to give the corresponding 1-acyldihydro-(2-thiazolyl)-thiazinones, (**20a** or **20b**). Their structures were confirmed by NMR spectrometry. A similar conversion of **20b** to thiazolylthiazinone with sulfur or DDQ was unsuccessful, and unchanged **20b** was recovered. Treatment of **20a** with DDQ in dichloromethane afforded the desired (2-thiazolyl)thiazinone (**21**) in good yield.

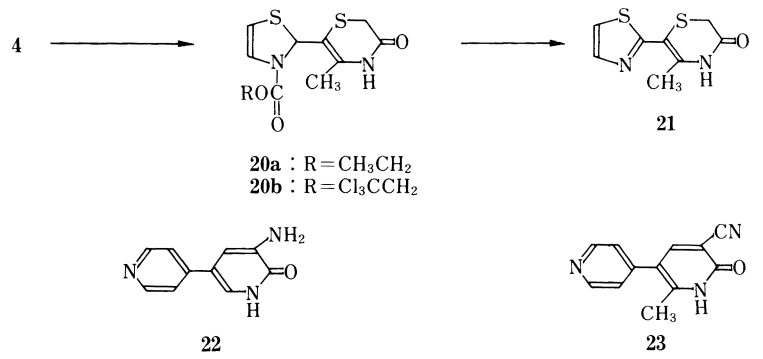


Chart 5

Biological Results

Much attention has recently been focused on the development of new cardiotonic agents, because there is a need for less toxic drugs than cardiac glycosides, which remain the basic agents for treatment of congestive heart failure.

Pyridylpyridine compounds such as amrinone (**22**) and milrinone (**23**)[8] have recently been developed as new cardiotonic agents, and their clinical usefulness has been proved. The structural similarity of these bi-heterocyclic compounds to the compounds described above

TABLE I. Effects of Thiazinone Derivatives on Developed Tension on the Guinea Pig Left Atrium[a]

Compd.[c]	Change in developed tension[b] (mg)
6a	511 ± 70
6b	426 ± 56
6c	278 ± 56
6d	194 ± 21
6e	214 ± 56
6f	0
6g	75 ± 21
11	0
14a	588 ± 30
14b	582 ± 44
14c	100 ± 50
16a	225 ± 123
16b	111 ± 34
19a	300 ± 125
19b	103 ± 41
21	97 ± 16

a) Suspended in Krebs–Henseliet solution bubbled with 95% O_2 and 5% CO_2 at 30 °C. *b*) The left atrium, whose resting tension was adjusted to 500 mg, was stimulated by square pulses of 5-ms duration, a voltage of 20% above the threshold and a stimulating rate of 0.5 Hz. Contractive forces were measured as absolute changes in developed tension. *c*) Concentration, 10^{-4} M in water, except for **16a** and **19a** (10^{-5} M).

prompted us to study their pharmacological activity, particularly in regard to cardiotonic activity.

We tested these compounds primarily for inotropic activity using the isolated left atria of guinea pig. The results of this screening are given in Table I. The most active compound was the unsubstituted pyridylthiazinone (**6a**) and the introduction of substituents into the pyridine ring of **6a** led to less active derivatives. Replacement of the pyridine ring of **6a** by pyridazine, quinoline or thiazole reduced the activity. Introduction of lower alkyl groups into the 2-position of the thiazinone ring as in **14a** and **14b** resulted in unchanged or somewhat enhanced activity. Piperazinylthiazinone (**11**) and pyridyl-4-methylthiazinone (**14c**) showed no activity.

Experimental

Melting points were determined on a Yamato MP-1 apparatus, and are uncorrected. NMR spectra were recorded on a JEOL FX-270 spectrometer with tetramethylsilane as the reference, and IR spectra were recorded on a Hitachi 260-10 spectrometer. The results of detailed characterization (yields, elemental analyses, IR, NMR spectra) of the bi-heterocyclic compounds reported here are summarized in Tables II and III. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 0.2 mm (E. Merck) and spots were detected under ultraviolet (UV) irradiation. Column chromatography was done on Wakogel C-200 and the developing solvents are shown in parentheses.

Thiazinones (4 and 12a—c)——5-Methyl-2*H*-1,4-thiazin-3(4*H*)-ones (**4**) were prepared by a procedure developed by Rao *et al.*[5] The 4-methyl derivative of **4** (**12c**) was synthesized from **4** by the method of deStevens *et al.*[6] Preparation of 2,5-dimethyl-2*H*-1,4-thiazin-3(4*H*)-one (**12a**) was carried out by a modification of the method of Rao *et al.*[5] as described below.

A mixture of ethyl α-mercaptopropionate (19.0 g, 141 mmol) and 28% ammonia (100 ml) was stirred at room temperature for 20 h under an N_2 atmosphere and then evaporated to dryness *in vacuo*, to give α-mercaptopropionamide as a colorless solid. A solution of monochloroacetone (13.9 g, 150.7 mmol) in Et_2O (40 ml) was added dropwise to a mixture of α-mercaptopropionamide and triethylamine (14.5 g, 143.4 mmol) in absolute EtOH over a period of 2 h at 0 °C with stirring, and the mixture was stirred at room temperature for 2 h, then evaporated at 50 °C *in vacuo*. The residue was dissolved in absolute EtOH (100 ml) and the solution was acidified to pH 1—2 by adding *p*-toluenesulfonic acid monohydrate portionwise with shaking. The mixture was stirred at 60—70 °C for 30 min and

TABLE II. Data for (1,4-Dihydro-4-pyridinyl)thiazinones and 1-Alkoxy Derivatives

Compd.	mp (°C) Recrystn. solvent	IR ν_{max}^{KBr} cm^{-1}	NMR ($CDCl_3$) δ [b]	Analysis (%) Calcd (Found)			Formula	Yield (%)
				C	H	N		
5a	158—160 (EtOH)	3200, 3100, 1720, 1670, 1630	1.99 (3H, s), 3.23 (2H, s), 4.16 (1H, m), 4.74—4.93 (2H+2H, m), 6.97 (2H, d, J=7 Hz), 7.26 (1H, br)	40.69 (40.62	3.41 3.37	7.29 7.02)	$C_{13}H_{13}Cl_3N_2O_3S$	81
5b	168.5—170 (EtOH)	3190, 3080, 1720, 1670, 1630	2.07 (3H, s), 3.28 (2H, s), 4.39 (1H, d, J=4 Hz), 4.75—5.06 (2H+1H, s+m), 7.10 (1H, d, J=8 Hz), 7.30 (1H, s), 8.38 (1H, s)	37.34 (37.12	2.89 2.78	6.70 6.67)	$C_{13}H_{12}Cl_4N_2O_3S$	66
5c	152—154 (AcOEt)	3230, 3120, 1735, 1690, 1650	1.65 (3H, s), 2.03 (3H, s), 3.21 (2H, ABq, J=14.6 Hz), 4.02 (1H, d, J=3 Hz), 4.74—4.96 (2H+1H, m), 6.80 (1H, d, J=6 Hz), 6.98 (1H, dd, J=6, 8 Hz), 8.04 (1H, s)	42.28 (42.07	3.80 3.77	7.04 6.81)	$C_{14}H_{15}Cl_3N_2O_3S$	32
5d	154—156 (EtOH)	3290, 3120, 1745, 1680, 1620	2.17 (3H, s), 3.14 (2H, s), 4.53 (1H, d, J=5 Hz), 4.99 (2H, s), 5.14 (1H, dd, J=5, 8 Hz), 7.13 (1H, dd, J=2, 8 Hz), 7.91 (1H, d, J=2 Hz), 8.23 (1H, s), 9.53 (1H, s)	40.84 (40.65	3.18 3.24	6.80 6.68)	$C_{14}H_{13}Cl_3N_2O_4S$	44
5e	188.5—190.5 (dec.) (EtOH)	3220, 3120, 2240, 1730, 1680, 1640	2.08 (3H, s), 3.30 (2H, ABq, J=15 Hz), 4.36 (1H, d, J=4.6 Hz), 4.78—5.02 (2H+1H, m), 7.00 (1H, d, J=8 Hz), 7.62 (1H, s), 7.84 (1H, s)	41.14 (41.05	2.95 2.91	10.28 10.10)	$C_{14}H_{12}Cl_3N_3O_3S$	63
5f	170—172 (EtOH)	3350, 3300, 1730, 1670, 1610	2.10 (3H, s), 3.16 (2H, s), 3.76 (3H, s), 4.47 (1H, d, J=4.4 Hz), 4.76—5.10 (2H+1H, m), 7.00 (1H, d, J=8 Hz), 7.82 (1H, s), 8.09 (1H, s)	40.78 (40.52	3.42 3.35	6.34 6.18)	$C_{15}H_{15}Cl_3N_2O_5S$	48
5g	141—142.5 (EtOH)	3200, 3060, 1730, 1660	2.13 (3H, s), 2.34 (3H, s), 3.12 (2H, ABq, J=14.6 Hz), 4.53 (1H, d, J=4.6 Hz), 4.80—5.13 (2H+1H, m), 7.00 (1H, d, J=8 Hz), 7.60 (1H, s), 8.03 (1H, s)	42.31 (42.08	3.55 3.59	6.58 6.37)	$C_{15}H_{15}Cl_3N_2O_4S$	46
13a	140—142 (column)	3200, 3080, 1720, 1670, 1630	1.40 (3H, d, J=7 Hz), 1.98 (3H, s), 3.33 (1H, q, J=7 Hz), 4.16 (1H, m), 4.70—4.94 (2H+2H, m), 6.95 (2H, d×2, J=8 Hz), 7.75 (1H, s)	42.28 (42.33	3.80 3.89	7.04 7.17)	$C_{14}H_{15}Cl_3N_2O_3S$	42
13b	121—122 (column)	3200, 3070, 1720, 1670, 1630	1.00 (3H, t, J=7 Hz), 1.66 (2H, m), 2.00 (3H, s), 3.10 (1H, dd, J=6, 8 Hz), 4.15 (1H, m), 4.60—5.00 (2H+2H, m+s), 7.05 (2H, d, J=8 Hz), 8.80 (1H, s)	43.75 (43.59	4.16 4.23	6.80 6.83)	$C_{15}H_{17}Cl_3N_2O_3S$	27

13c	Oil	1720, 1690, 1660[a]	2.10 (3H, s), 3.28 (3H, s), 3.41 (2H, s), 4.16 (1H, m), 4.75—4.94 (2H+2H, m), 6.98 (2H, d, J=8.8 Hz)				$C_{14}H_{15}Cl_3N_2O_3S$	33
15a	156—157· (MeOH)	3200, 3090, 1740, 1690	2.03 (3H, s), 3.25 (2H, ABq, J=15 Hz), 4.06 (1H, m), 4.85—5.00 (2H+1H, m), 6.83 (1H, m), 7.22 (1H, d, J=8 Hz), 8.44 (1H, s)	37.46 (37.21	3.14 3.08	10.92 10.80)	$C_{12}H_{12}Cl_3N_3O_3S$	63
15b	200—203 ($CHCl_3$–MeOH)	3200, 3070, 1720, 1670, 1635	1.92 (3H, s), 1.98 (3H, s), 3.17 (2H, ABq, J=15 Hz), 4.20 (1H, d, J=4 Hz), 4.94 (1H, dd, J=4, 8 Hz), 5.03 (2H, s), 7.17 (1H, d, J=8 Hz), 9.64 (1H, s)[c]	39.16 (39.27	3.53 3.60	10.54 10.73)	$C_{13}H_{14}Cl_3N_3O_3S$	26
17a	168—170 (EtOH)	3200, 3060, 1710, 1660, 1630	2.13 (3H, s), 3.12 (2H, ABq, J=14.4 Hz), 4.62 (1H, d, J=4 Hz), 4.93 (2H, s), 5.20 (1H, dd, J=4, 8 Hz), 7.09—7.33 (3H, m), 7.21 (1H, d, J=8 Hz), 7.90 (1H, s), 8.10 (1H, d, J=8.8 Hz)	47.07 (46.79	3.48 3.45	6.46 6.38)	$C_{17}H_{15}Cl_3N_2O_3S$	24
17b	181.5—183 (EtOH)	3200, 3050, 1720, 1670	2.13 (3H, s), 3.12 (2H, ABq, J=15 Hz), 3.79 (3H, s), 4.61 (1H, d, J=4 Hz), 4.92 (2H, s), 5.16 (1H, dd, J=4, 8 Hz), 6.61 (1H, d, J=3 Hz), 6.84 (1H, dd, J=3, 9 Hz), 7.20 (1H, d, J=8 Hz), 8.04 (1H, d, J=9 Hz), 8.06 (1H, s)	46.61 (46.38	3.69 3.71	6.04 5.94)	$C_{18}H_{17}Cl_3N_2O_4S$	32
18a	199.5—200 (EtOH)	3200, 3100, 1730, 1680, 1640	2.22 (3H, s), 3.02 (2H, s), 4.93 (2H, ABq, J=12 Hz), 5.83 (1H, dd, J=6, 9 Hz), 6.13 (1H, d, J=6 Hz), 6.66 (1H, d, J=9 Hz), 7.03—7.85 (4H, m), 9.51 (1H, s)	47.07 (46.63	3.48 3.49	6.46 6.36)	$C_{17}H_{15}Cl_3N_2O_3S$	6
18b	179—181 (EtOH)	3180, 3070, 1700, 1670, 1630	2.23 (3H, s), 3.03 (2H, s), 3.86 (3H, s), 4.90 (2H, ABq, J=12 Hz), 5.94 (1H, dd, J=6, 9 Hz), 6.16 (1H, d, J=6 Hz), 6.66 (1H, d, J=9 Hz), 6.76 (1H, d, J=3 Hz), 6.93 (1H, dd, J=3, 9 Hz), 7.64 (1H, d, J=9 Hz), 8.57 (1H, s)	46.61 (46.25	3.69 3.54	6.04 5.94)	$C_{18}H_{17}Cl_3N_2O_4S$	26
20a	146—147 ($EtOH–H_2O$)	3220, 3130, 1700, 1680, 1640, 1600	1.30 (3H, t, J=7 Hz), 2.13 (3H, s), 3.25 (2H, s), 4.25 (2H, q, J=7 Hz), 5.62 (1H, d, J=5 Hz), 6.53 (1H, d, J=5 Hz), 6.62 (1H, s), 8.57 (1H, s)	46.13 (45.97	4.92 4.98	9.78 9.74)	$C_{11}H_{14}N_2O_3S_2$	24
20b	141—143 (dec.) ($EtOH–H_2O$)	3200, 3100, 1740, 1680, 1630, 1600	2.14 (3H, s), 3.21 (2H, s), 4.80 (2H, s), 5.67 (1H, d, J=4.4 Hz), 6.55 (1H, d, J=4.4 Hz), 6.61 (1H, s), 8.10 (1H, s)	33.90 (33.75	2.84 2.80	7.18 7.15)	$C_{11}H_{11}Cl_3N_2O_3S_2$	34

a) Measured as liquid. *b*) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. *c*) Measured as a solution in DMSO-d_6.

TABLE III. Data for 6-Substituted Thiazinones

Compd.	mp (°C). Recrystn. solvent	IR ν_{max}^{KBr} cm^{-1}	NMR ($CDCl_3$) δ [a]	Analysis (%) Calcd (Found) C	H	N	Formula	Yield (%)
6a	187—188.5 (DMF–H_2O)	3200, 3050, 1680, 1580	2.06 (3H, s), 3.44 (2H, s), 7.30 (2H, dd, J=1.5, 5 Hz), 8.60 (2H, d, J=5 Hz), 8.70 (1H, s)	58.22 (58.48)	4.88 4.99	13.58 13.53)	$C_{10}H_{10}N_2OS$	77
6b	169—171 (EtOH–H_2O)	3200, 3080, 1630, 1570	1.85 (3H, s), 3.49 (2H, s), 7.30 (1H, d, J=5 Hz), 8.59 (1H, d, J=5 Hz), 8.76 (1H, s), 9.00 (1H, s)	49.89 (49.68)	3.76 3.76	11.64 11.65)	$C_{10}H_9ClN_2OS$	58
6c	185—187 (EtOH)	3040, 1670, 1630, 1590	1.78 (3H, s), 2.31 (3H, s), 3.44 (2H, s), 7.09 (1H, d, J=5 Hz), 8.44 (1H, d, J=5 Hz), 8.51 (1H, s), 8.58 (1H, s)	59.97 (59.62)	5.49 5.50	12.71 12.51)	$C_{11}H_{12}N_2OS$	85
6d	152—154 (CH_3CN)	3180, 3060, 1660, 1620	1.85 (3H, s), 3.52 (2H, s), 7.32 (1H, d, J=5.4 Hz), 8.45 (1H, s), 8.80 (1H, d, J=5.4 Hz), 9.11 (1H, s), 10.23 (1H, s)	56.39 (56.43)	4.30 4.31	11.95 11.85)	$C_{11}H_{10}N_2O_2S$	10
6e	140—141 (EtOH)	3170, 3050, 2230, 1680, 1600	1.95 (3H, s), 3.50 (2H, s), 7.38 (1H, d, J=5.4 Hz), 8.65 (1H, s), 8.90 (1H, d, J=5.4 Hz), 8.93 (1H, s)	57.12 (57.17)	3.92 3.89	18.17 18.14)	$C_{11}H_9N_3OS$	35
6f	177—178 (EtOH)	3300, 1710, 1680, 1620	1.83 (3H, s), 3.46 (2H, s), 3.94 (3H, s), 7.21 (1H, d, J=5.4 Hz), 8.33 (1H, s), 8.72 (1H, d, J=5.4 Hz), 9.12 (1H, s)	54.53 (54.34	4.57 4.51	10.60 10.39)	$C_{12}H_{12}N_2O_3S$	40
6g	160—161.5 (ab. EtOH)	3200, 1680, 1620	1.84 (3H, s), 2.61 (3H, s), 3.43 (2H, s), 7.23 (1H, d, J=5 Hz), 8.27 (1H, s), 8.69 (1H, d, J=5 Hz), 8.88 (1H, s)	58.04 (57.90	4.87 4.69	11.28 11.01)	$C_{12}H_{12}N_2O_2S$	10
11	180—195 (dec.)	3300, 3200, 3050, 1680, 1640	1.50—1.75 (5H, m), 1.97 (3H, s), 2.52—2.70 (3H, m), 3.11—3.17 (2H, m), 3.17 (2H, s), 8.25 (1H, s)	56.56 (57.05	7.59 7.40	13.19 13.10)	$C_{10}H_{16}N_2OS$	36
14a	144—146 (column)	3200, 3090, 1680, 1620	1.53 (3H, d, J=7 Hz), 2.05 (3H, s), 3.53 (1H, q, J=7 Hz), 7.28 (2H, dd, J=1.6, 4.6 Hz), 7.40 (1H, s), 8.61 (2H, d, J=4.6 Hz)	59.97 (59.76	5.49 5.55	12.71 12.55)	$C_{11}H_{12}N_2OS$	52
14b	122—124 (EtOH–H_2O)	3210, 3100, 1670	1.14 (3H, t, J=7.3 Hz), 1.76 (1H, m), 1.99 (1H, m), 2.03 (3H, s), 3.28 (1H, dd, J=6, 9 Hz), 7.27 (2H, dd, J=1.7, 5 Hz), 8.52 (1H, s), 8.61 (2H, d, J=5 Hz)	61.50 (61.63	6.02 6.05	11.95 11.59)	$C_{12}H_{14}N_2OS$	21
14c	139—140 (column)	1660, 1600	2.10 (3H, s), 3.28 (3H, s), 3.41 (2H, s), 7.32 (2H, dd, J=1.5, 5 Hz), 8.62 (2H, d, J=5 Hz)	59.97 (59.70	5.49 5.35	12.71 12.40)	$C_{11}H_{12}N_2OS$	14
16a	231—233 (MeOH)	3200, 3050, 1670, 1600	1.99 (3H, s), 3.46 (2H, s), 7.65 (1H, dd, J=2.4, 5 Hz), 9.20 (1H, dd, J=1, 5 Hz), 9.25 (1H, dd, J=1, 2.4 Hz), 10.18 (1H, s)[b]	52.15 (51.93	4.37 4.27	20.27 20.05)	$C_9H_9N_3OS$	23
16b	187—188 (ab. EtOH)	3200, 3050, 1670, 1620	1.81 (3H, s), 2.75 (3H, s), 3.46 (2H, s), 7.26 (1H, d, J=5 Hz), 8.24 (1H, s), 9.10 (1H, d, J=5 Hz)	54.27 (54.14	5.01 4.76	18.99 18.72)	$C_{10}H_{11}N_3OS$	36
19a	173.5—174 (MeOH)	3200, 3100, 1680, 1640	1.77 (3H, s), 3.56 (2H, s), 7.35 (1H, d, J=4.4 Hz), 7.60 (1H, dd, J=7.8, 8.3 Hz), 7.75 (1H, dd, J=7.8, 8.3 Hz), 7.94 (1H, d, J=8.3 Hz), 7.95 (1H, s), 8.15 (1H, d, J=8.3 Hz), 8.95 (1H, d, J=4.4 Hz)	65.59 (65.45	4.71 4.63	10.93 10.82)	$C_{14}H_{12}N_2OS$	25
19b	183—184 (EtOH)	3200, 3100, 1680	1.82 (3H, s), 3.55 (2H, ABq, J=15 Hz), 3.94 (3H, s), 7.15 (1H, d, J=3 Hz), 7.28 (1H, d, J=4.4 Hz), 7.41 (1H, dd, J=3, 9 Hz), 8.06 (1H, d, J=9 Hz), 8.31 (1H, s), 8.78 (1H, d, J=4.4 Hz)	62.91 (62.90	4.92 4.76	9.78 9.57)	$C_{15}H_{14}N_2O_2S$	32
21	233—235 (dec.) (MeOH)	3200, 3080, 1680, 1615	2.38 (3H, s), 3.43 (2H, s), 7.72 (1H, d, J=3.4 Hz), 7.86 (1H, d, J=3.4 Hz), 10.15 (1H, s)[b]	45.26 (45.28	3.79 3.85	13.19 13.25)	$C_8H_8N_2OS_2$	54

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. *b*) Measured as a solution in DMSO-d_6.

then evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate–hexane = 1 : 1) to give **12a** (3.9 g, 19.2%) as a colorless powder, mp 78—80 °C. NMR ($CDCl_3$) δ: 1.44 (3H, d, J = 7 Hz), 1.95 (3H, s), 3.35 (1H, q, J = 7 Hz), 5.21 (1H, s), 8.07 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3200, 3100, 1670, 1630. *Anal.* Calcd for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.06; H, 6.47; N, 9.62.

The synthesis of 2-ethyl-5-methyl-2*H*-1,4-thiazin-3(4*H*)-one (**12b**) was carried out as follows. α-Bromo-*n*-butyryl bromide (18.4 g, 80.2 mmol) was added dropwise to vigorously stirred 28% ammonia (33 ml) at −10 °C and the resulting precipitates were collected by filtration and washed with water to give α-bromo-*n*-butyramide (9.57 g, 72%) as a colorless powder. A mixture of α-bromo-*n*-butyramide (1.66 g, 10.0 mmol) and potassium ethylxanthate (1.6 g, 10.0 mmol) in acetone (20 ml) was stirred at room temperature for 2 h.

The insoluble material was filtered off, and the filtrate was concentrated *in vacuo*. The resulting syrupy xanthate was dissolved in benzene (15 ml) and, after the addition of morpholine (1.7 g, 19.5 mmol), the mixture was refluxed for 2 h. The mixture was then evaporated *in vacuo* to give α-mercapto-*n*-butyramide as a colorless solid, which was used in the next reaction without further purification.

The α-mercapto-*n*-butyramide thus obtained was treated with triethylamine (0.94 g, 9.4 mmol) and monochloroacetone (0.93 g, 10.0 mmol) and worked-up in the same manner as described for **12a** to give **12b** (1.21 g, 77%) as a colorless powder, mp 69—71 °C. NMR ($CDCl_3$) δ: 1.04 (3H, d, J = 8 Hz), 1.65—1.90 (2H, m), 1.93 (3H, s), 3.12 (1H, dd, J = 6, 9 Hz), 5.14 (1H, s), 7.92 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3200, 3100, 2950, 1680. *Anal.* Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.90. Found: C, 53.51; H, 7.28; N, 8.86.

5-Methyl-6-(1-ethoxycarbonyl-1,4-dihydro-4-pyridyl)-1,4-thiazin-3(4*H*)-one (9a) and the (1-Butoxycarbonyl) Analog (9b)——Ethyl chloroformate (4.78 ml, 50 mmol) was added dropwise to a stirred solution of pyridine (4.85 ml, 60 mmol) in acetonitrile (21 ml) at 0 °C and the mixture was stirred at the same temperature for 10 min. Compound **4** (0.65 g, 5 mmol) was then added portionwise, and the reaction mixture was stirred at 0 °C for 20 min and then at room temperature for 5 h. The mixture was evaporated to dryness *in vacuo* and the residue was dissolved in $CHCl_3$, washed with 2 N HCl solution and then with water, and dried over anhydrous $MgSO_4$. The product obtained by removal of the solvent *in vacuo* was chromatographed on silica gel (ethyl acetate–hexane = 2 : 1) then recrystallized from EtOH to give **9a** (0.39 g, 27.7%) as pale yellow needles, mp 145.5—146 °C. NMR ($CDCl_3$) δ: 1.33 (3H, t, J = 7 Hz), 2.00 (2H, s), 3.25 (2H, s), 4.21 (1H, d, J = 3 Hz), 4.32 (2H, q, J = 7 Hz), 4.75 (2H, dd, J = 3, 8 Hz), 7.02 (2H, d, J = 8 Hz), 8.90 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3200, 3090, 2990, 2920, 1725, 1680, 1640. *Anal.* Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.69; H, 5.75; N, 9.99. Found: C, 55.44; H, 5.80; N, 9.74.

By using di-*tert*-butyl dicarbonate instead of ethyl chloroformate, the 1-butoxycarbonyl analog (**9b**) was synthesized in the same manner in 17% yield as pale yellow needles, mp 155—158 °C.

5-Methyl-6-(4-pyridyl)-2*H*-1,4-thiazin-3(4*H*)-one (6a) and Its Analogs (6b—e and 14a—b)——A mixture of **5a** (300 g, 782.3 mmol), sublimed sulfur (150 g, 4.69 mmol) and dimethylformamide (DMF) (1.5 l) was refluxed for 1.5 h. The mixture was evaporated to dryness *in vacuo*, and the residue was extracted with 2 N HCl solution. The insoluble material was filtered off and the filtrate was washed with $CHCl_3$ and neutralized with 2 N NaOH solution below 0 °C. The resulting precipitates were collected and washed with water. Recrystallization from DMF–H_2O gave **6a** (124 g, 77%) as pale yellow prisms.

Concentrated HCl (14 ml) was added dropwise to a suspension of **6a** (20.5 g, 99.5 mmol) in MeOH–H_2O (500 ml, 3 : 2, v/v) and the mixture was stirred at room temperature for 0.5 h. The solvent was evaporated off *in vacuo* and the residue was washed with acetone (200 ml) and recrystallized from EtOH to give the hydrochloride of **6a** (21 g, 87%) as yellow needles, mp >250 °C (dec.). *Anal.* Calcd for $C_{10}H_{10}N_2OS \cdot HCl$: C, 49.48; H, 4.56; N, 11.54. Found: C, 49.44; H, 4.66; N, 11.64.

The sulfate [yellow needles from EtOH, mp 242—243 °C (dec.)] and the tosylate [yellow needles from EtOH, mp 205—206 °C (dec.)] were analogously obtained. Compounds **6b—e** and **14a—b** were also obtained in the above manner. The yields, melting points, spectral data and elemental analyses are given in Table III.

5-Methyl-6-(3-methoxycarbonyl-4-pyridyl)-2*H*-1,4-thiazin-3(4*H*)-one (6f) and Its 3-Acetylpyridyl Analog (6g)——A suspension of **5f** (2.1 g, 4.8 mmol) and zinc powder (1.5 g, 22.9 mmol) in THF–H_2O (60 ml, 1 : 1, v/v) was stirred at 60 °C for 2 h. After addition of zinc powder (0.5 g, 7.6 mmol), the mixture was further stirred at the same temperature for 2 h, then allowed to cool. The insoluble material was filtered off and washed with THF–H_2O (1 : 1, v/v). The combined filtrate and washings were extracted with benzene. The extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo* to give **10f** (0.76 g, 60% as a pale yellow powder, mp 176—177 °C which was submitted to the next reaction without further purification. NMR (DMSO-d_6) δ: 1.91 (3H, s), 3.05 (2H, ABq, J = 14 Hz), 3.54 (3H, s), 4.39 (1H, d, J = 5 Hz), 4.45 (1H, dd, J = 5, 8 Hz), 6.14 (1H, dd, J = 6, 8 Hz), 7.24 (1H, d, J = 6 Hz), 8.30 (1H, br), 9.34 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3200, 1620, 1600.

In an analogous manner, **10g**, was synthesized in 55% yield as pale yellow needles, mp 203—205 °C (dec.). NMR (DMSO-d_6) δ: 1.93 (3H, s), 2.05 (3H, s), 2.96 (2H,s), 4.43 (1H, d, J = 5 Hz), 4.60 (1H, dd, J = 5, 7 Hz), 6.16 (1H, dd, J = 5, 7 Hz), 7.43 (1H, d, J = 6 Hz), 8.43 (1H, m), 9.30 (1H, s).

A suspension of **10f** (0.76 g, 2.9 mmol) and DDQ (0.65 g, 2.9 mmol) in acetonitrile (30 ml) was stirred at 50 °C for 2 h, then allowed to cool. The insoluble material was filtered off and the filtrate off and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$–MeOH = 20 : 1) and recrystallized from

EtOH to give **6f** (0.48 g, 62.3%) as pale yellow needles, mp 177—178 °C.

Compound **6g** was synthesized analogously. The yields, spectral data and elemental analyses are given in Table III.

5-Methyl-6-(4-piperidyl)-2*H*-1,4-thiazin-3(4*H*)-one (11)——Zinc powder (1.7 g, 26 mmol) was added to a stirred solution of **5a** (1 g, 2.6 mmol) in formic acid (14 ml) and the mixture was stirred at room temperature for 3 h. The insoluble materials were filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water (30 ml) and the resulting solution was adjusted to pH 7.0 with 1 N NaOH solution and then extracted with $CHCl_3$. The extracts were worked-up in a usual manner and chromatographed on silica gel ($CHCl_3$–MeOH) to give **6a** (20 mg, 3.7%).

The aqueous solution was adjusted to pH 12 with 1 N NaOH solution and extracted three times with 50 ml portions of $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo* to give **11** (200 mg, 36.2%) as a pale yellow powder, mp 180—195 °C (dec.). NMR ($CDCl_3$) δ: 1.65 (5H, m), 1.97 (3H, s), 2.60 (3H, m), 3.15 (4H, s+t), 8.25 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3300, 3200, 3050, 1680, 1640. *Anal.* Calcd for $C_{10}H_{16}N_2OS$: C, 57.12; H, 4.79; N, 13.32. Found: C, 57.05; H, 4.40; N, 13.10.

5-Methyl-6-(4-pyridazinyl)-2*H*-1,4-thiazin-3(4*H*)-one (16a) and Its 3-Methylpyridazinyl Analog (16b)——A mixture of pyridazine (1.44 g, 19.8 mmol), 2,2,2-trichloroethyl chloroformate (3.44 ml, 25.0 mmol), **4** (1.29 g, 10.5 mmol) and acetonitrile (40 ml) was treated in the same manner as described for **5a**. After work-up, the crude product was chromatographed on silica gel (ethyl acetate–hexane = 1 : 1) and recrystallized from MeOH to give **15a** (2.4 g, 63%) as colorless needles. Compound **15b** was analogously obtained from 3-methylpyridazine.

A mixture of 15a (3.11 g, 8.1 mmol), sublimed sulfur (1.5 g, 46.9 mmol) and DMF (15 ml) was treated in the same manner as described for **6a**. Recrystallization from MeOH gave **16a** (1.02 g, 23%) as pale yellow plates.

Compound **16b** was also analogously obtained. The yields, melting points, spectral data and elemental analyses are given in Tables II and III.

5-Methyl-6-(4-quinolyl)-2*H*-1,4-thiazin-3(4*H*)-one (19a) and Its 6-Methoxyquinolyl Derivative (19b)——A mixture of quinoline (10.0 g, 78.0 mmol), 2,2,2-trichloroethyl chloroformate (16.4 g, 78.0 mmol), **4** (5 g, 39.0 mmol) and acetonitrile (250 ml) were treated in the same manner as described for **5a**. The crude product was chromatographed on silica gel to give **17a** (4.0 g, 24%) as pale yellow plates, mp 168—170 °C (from EtOH) and then **18a** (1.0 g, 6%) as pale yellow plates, mp 199.5—200 °C (from EtOH). The *Rf* values on TLC (ethyl acetate–hexane = 2 : 3) were 0.38 for **17a** and 0.48 for **18a**. Compounds **17b** and **18b** were obtained in the same manner.

A mixture of **17a** (4.0 g, 9.2 mmol), sublimed sulfur (2.5 g, 78.1 mmol) and DMF (15 ml) was refluxed for 3.5 h and then treated in the same manner as described for **6a**. The crude product was chromatographed on silica gel ($CHCl_3$–MeOH = 20 : 1) and recrystallized from MeOH to give **19a** (600 mg, 25%) as colorless leaflets.

Compound **19b** was also obtained in the same manner. The yields, melting points, spectral data and elemental analyses are given in Tables II and III.

5-Methyl-6-(2-thiazolyl)-2*H*-1,4-thiazin-3(4*H*)-one (21)——Ethyl chloroformate (3.6 g, 33.2 mmol) was added dropwise to a stirred solution of thiazole (5.7 g, 67.0 mmol) in CH_2Cl_2 (72 ml) under ice-cooling and the mixture was stirred at 0 °C for 0.5 h. Compound **4** (3.6 g, 27.9 mmol) was added, and the mixture was stirred at room temperature for 5 h. The solution was washed with 2 N HCl solution and then with water, dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate–hexane = 1 : 1), then recrystallized from EtOH to give **20a** (1.9 g, 24%) as colorless needles.

By using 2,2,2-trichloroethyl chloroformate instead of ethyl chloroformate, **20b** was analogously obtained.

DDQ (159 mg, 0.7 mmol) was added portionwise to a stirred solution of **20a** (200 mg, 0.7 mmol) in CH_2Cl_2 (2 ml) and the mixture was stirred at room temperature for 1.5 h. The resulting precipitates were collected and washed with saturated K_2CO_3 solution and then with water. Recrystallization from MeOH gave **21** (80 mg, 54%) as colorless needles. The melting points, spectral data and elemental analyses are given in Tables II and III.

Biological Method——We determined inotropic activity using male Hartley guinea pig left atrium suspended in Krebs–Henseleit solution (gassed with 95% O_2/5% CO_2) at 30 °C. Resting tension was adjusted to 500 mg after 1 h of equilibration. The atrium was stimulated by square pulses of 5 ms duration at a voltage of 20% above threshold and a stimulating rate of 0.5 Hz. Test drug was added to the bathing fluid at 30 min intervals. Fifteen minutes after the maximum effect had been achieved, the atrium was washed with three changes of drug-free medium until the basal developed tension of the atrium was recorded isometrically on a rectilinear recorder *via* a force displacement transducer (Nihon Koden, TB-611T, Tokyo, Japan). Change of contractile force was measured as an absolute change in developed tension.

The test materials were dissolved in 0.2 N HCl to provide 3×10^{-2} M solutions, 0.1 ml aliquots of which were added to 30 ml of the bathing fluid.

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