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Studies on the Synthesis of Condensed Heterocyclic Isoquinolone Derivatives. I. Studies on the Synthesis and Pharmacology of Thiazino, Oxazino and Pyrimido Isoquinolones

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5-Oxo-1,2,3,5-tetrahydro-5H-imidazo[1,2-*b*]isoquinoline (IIa) and related compounds were synthesized from homophthalic acid and an aliphatic 1,2- or 1,3-diamine. In addition, homophthalic acids or *o*-carboxyphenylmalonic acid diesters were allowed to react with an aliphatic 1,2- or 1,3-aminoalcohol or aminothiol with heating in the presence of *p*-toluenesulfonic acid, yielding a series of oxazolo- or oxazino-isoquinolones (VI) or thiazolo- or thiazino-isoquinolones (IV). Oxidation of IV gave the corresponding sulfoxides (VII) and sulfones (VIII). Treatment of *o*-cyanomethylbenzenesulfonyl chloride with an N-alkyl 1,2- or 1,3-diamine gave N-alkyl-imidazo- or pyrimido-benzothiazine-5,5-dioxide (XI).

The compounds thus prepared were evaluated for their anti-inflammatory effect in rats, using the carrageenin paw edema method, and some of the condensed heterocyclic isoquinolone derivatives were found to exhibit strong anti-inflammatory activity. These compounds were also examined for analgesic activity in terms of the inhibition of acetic acid induced writhing. Compound VIIIk showed stronger anti-inflammatory activity than phenylbutazone, as well as analgesic activity comparable to that of aminopyrine, and had very low toxicity.

Keywords——anti-inflammatory activity; analgesic activity; thiazolo[3,2-*b*]isoquinolone; thiazino[3,2-*b*]isoquinolone; imidazo[3,2-*b*]isoquinolone; oxazolo[3,2-*b*]-isoquinolone; oxazino[3,2-*b*]isoquinolone; imidazo[3,2-*b*](1,2)benzothiazine-5,5-dioxide; structure- activity relationship

In previous papers,[2] we reported on the synthesis and pharmacological activities of a series of compounds having pyridone structures. In the present work, a series of condensed heterocyclic isoquinolone derivatives was synthesized and the pharmacology of these compounds was investigated. It has been found that thiazino isoquinolones show strong anti-inflammatory and analgesic activities, and have very low toxicity.

Synthesis

5-Oxo-1,2,3,5-tetrahydro-5H-imidazo[1,2-*b*]isoquinolines IIa,[3a] b and c were synthesized by the reaction of homophthalic acid (I) with aliphatic 1,2- or 1,3-diamine in *o*-dichloro benzene with heating according to the method of Nagarajan *et al.*[3b]

5-Oxo-2,3-dihydro-5H-thiazolo[3,2-*b*]isoquinoline (IVa)[4] was prepared from I by allowing it to react with 2-aminoethanethiol in the presence of sodium acetate in boiling acetic acid.

1) Location: *1-1-8, Azusawa, Itabashi-ku, Tokyo.*
2) Part I: K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, H. Arima, and M. Murakami, *Yakugaku Zasshi*, **99**, 588 (1979); Part II: K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *Chem. Pharm. Bull.* (Tokyo), **27**, 1207 (1979); Part III: K. Kubo, N. Ito, Y. Isomura, I. Sizu, H. Homma, and M. Murakami, *Yakugaku Zasshi*, **99**, 788 (1979); Part IV: K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *Yakugaku Zasshi*, **99**, 880 (1979).
3) *a*) E. Schefczik, *Ann. Chem.*, **729**, 83 (1969); *b*) K. Nagarajan, V.R. Rao, and R.K. Shah, *J. Indian Chem. Soc.*, 663 (1970).
4) E. Schefczik, *Ger. Patent* 1960376 (1971) [*C.A.*, 75, 63774*z* (1971)].

When treated with 3-aminopropanethiol, however, I afforded 6-oxo-3,4-dihydro-2H,6H-thiazino[3,2-*b*]isoquinoline (IVf) and N-γ-mercaptopropylhomophthalimide (III) in 18.5% and 32% yields, respectively. Compound III showed the parent ion at *m/e* 235 in the mass spectrum (MS) and one proton signal due to a thiol group (1.5 ppm, t), three methylene group signals (1.96 ppm, m, 2.56 ppm, t of t, 4.10 ppm, t) and one methylene group signal at the 4-position (4.04 ppm, s) in the nuclear magnetic resonance (NMR) spectrum. These spectral data support the structure III. The MS (*m/e*: 217 M^+) and microanalysis results for IVf indicated the molecular formula $C_{12}H_{11}NOS$. The NMR spectrum of IVf showed three methylene group signals due to the thiazino ring (2.1—2.4 ppm, 3.1 ppm, 4.2 ppm), one olefinic proton signal at the 11-position (6.5 ppm) and one aromatic proton signal (8.3—8.5 ppm) shifted to lower field by the anisotropy effect of a carbonyl group. These data are consistent with the structure IVf.

When I was allowed to react with 3-aminopropanethiol in *o*-dichlorobenzene at 140—150°, with removal of water by azeotropic distillation, III was obtained in 76% yield. Treatment of III with *p*-toluenesulfonic acid in *o*-dichlorobenzene at 90—120° afforded IVf in 68% yield.

When oxidized with hydrogenperoxide in acetic acid, IVf gave the corresponding sulfoxide (VIIe) at room temperature and the corresponding sulfone (VIIId) at 70—80°.

Schefczik[4] prepared N-hydroxyethylhomophthalimide (V) from I by allowing it to react with 2-aminoethanol in the presence of acetic acid in boiling xylene.

When I was allowed to react with 2-aminoethanol in the presence of *p*-toluenesulfonic acid as described for the synthesis of IVf, however, 5-oxo-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinoline (VIa) was obtained in good yield. The structure of VIa was determined on the basis of the microanalysis data and the NMR spectrum, which was similar to that of IVa. A similar reaction of I and 3-aminopropanol gave VIc.

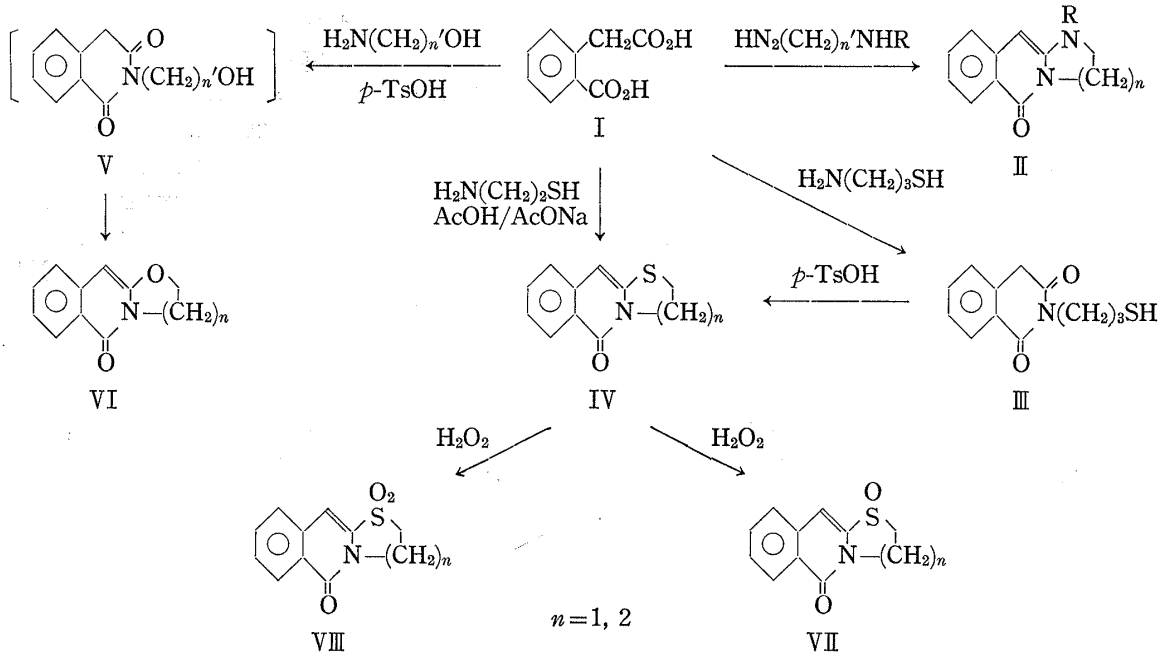
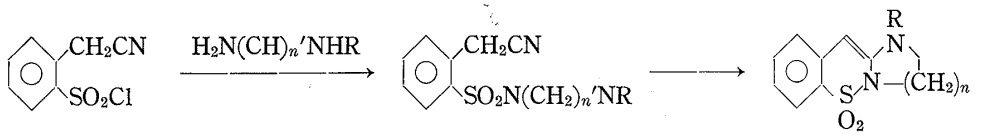


Chart 1

N-Alkyl-2,3-dihydro-1H-imidazo[1,2-*b*](1,2)benzothiazine-5,5-dioxides (XI) (compounds related to II, having a sulfoneamide bond instead of the amide bond of II) were also synthesized. Thus, treatment of *o*-chlorosulfonyl benzylcyanide (IX)[5] with an excess of N-ethylethylenediamine at −15° gave XIa, mp 123—124°, in 35% yield. On the basis of the MS (*m/e*: 250, M^+) and microanalysis data, XIa was assigned the formula $C_{12}H_{14}N_2O_2S$. The infrared (IR) spectrum showed an absorption band of the sulfoneamide group at 1310

cm^{-1} and the NMR spectrum showed one proton signal at the 10-position (5.1 ppm), one aromatic proton signal at the 5-position (7.7—7.8 ppm) and two methylene group signals (3.2—3.5 ppm, t, 3.8—4.0 ppm). Thus XIa was concluded to be 1-ethyl-2,3-dihydro-1H-imidazo[3,2-*b*](1,2)benzothiazine-5,5-dioxide. When IX was treated with one molar equivalent of N-ethylethylenediamine, *o*-(N-ethylaminoethylaminosulfonyl)benzylcyanide (Xa) was obtained. The structure of Xa was evident from the microanalysis data, MS (*m/e*: 267, M^+), the presence of an absorption band of the cyano group (2250 cm^{-1}) in the IR spectrum and the presence of a benzyl proton signal (4.48 ppm) in the NMR spectrum. On treatment with triethylamine in methanol, Xa was converted to XIa



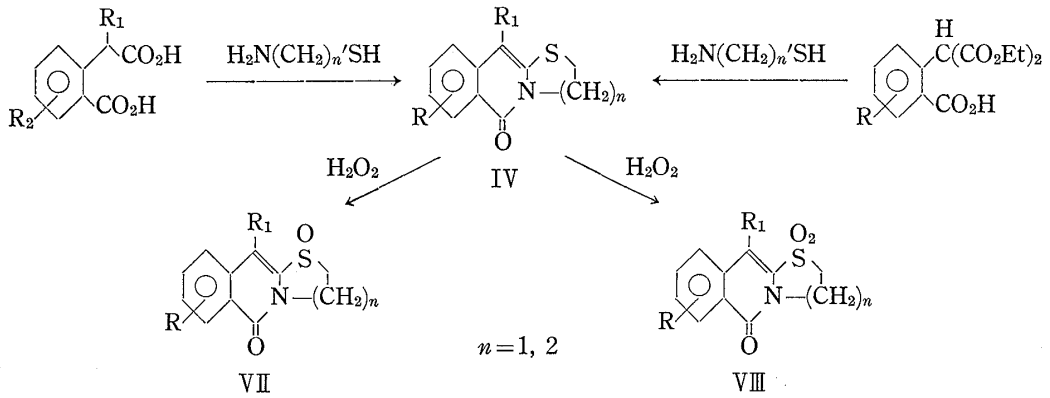
IX X XIa, b, c

XIa: R=C_2H_5, n=1
XIb: R=CH_3, n=1
XIc: R=CH_3, n=2

Chart 2

The pharmacological activities of the compounds thus prepared were studied. IVf VIIe, and VIIId showed strong anti-inflammatory and analgesic activities, and had low toxicity. In order to obtain more potent compounds, some modifications of these compounds were carried out. Homophthalic acids having alkyl, benzyl or phenyl groups at the α-position were prepared to introduce a substituent at the 4-position of the isoquinolone moiety. Homophthalic acids having nitro, amino, alkyl, alkoxy and halogen groups on the benzene ring were also synthesized. These homophthalic acid derivatives were heated with an aliphatic 1,2- or 1,3-aminothiol in *o*-dichlorobenzene, removing water by azeotropic distillation, and then *p*-toluenesulfonic acid was added to the reaction mixture to give a series of thiazino or thiazolo isoquinolone derivatives (IV). Oxidation of the compounds thus obtained with hydrogenperoxide gave the corresponding sulfoxides (VII) and sulfones (VIII).

Compounds IVw—y were also prepared by the reaction of *o*-carboxyphenylmalonic acid diester derivatives[6] with an aliphatic 1,2- or 1,3-aminothiol, followed by deethoxycarbonylation. Data for compounds II, IV, VII and VIII are listed in Table I and data for XI are listed in Table II.

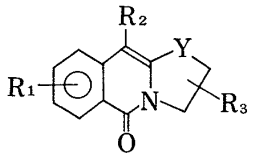


VII VIII

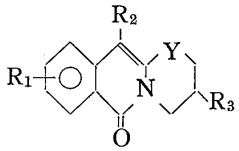
Chart 3

5) E. Sianesi, R. Redaelli, M. Bertani, and P. Da Re, *Chem. Ber.*, **103**, 1992 (1970).
6) A. Brugginik and A. Mekillor, *Tetrahedron*, **3**, 2697 (1975).

TABLE I.



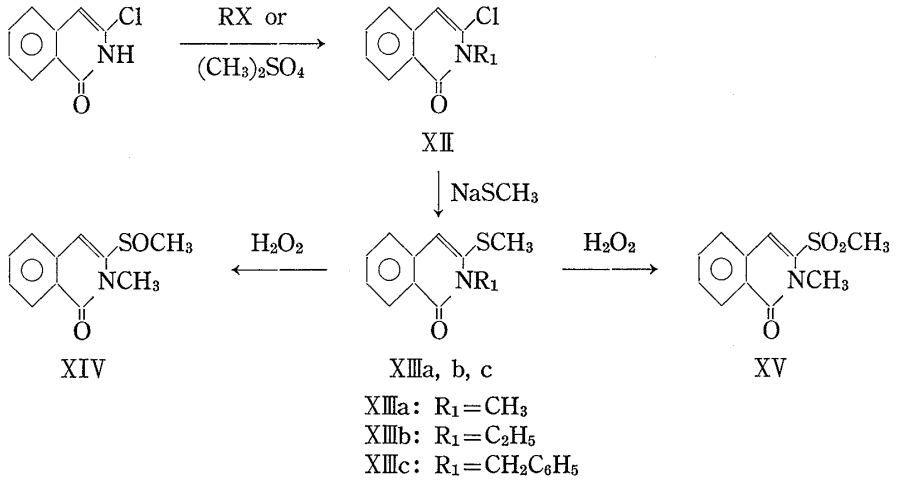
Compd. No.	Y	R_1	R_2	R_3	Antiinf. activity[a] (25 mg/kg)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	NH	H	H	H	*[b]	207—212[e]	AcOH–H_2O	95	$C_{11}H_{10}N_2$	77.62	5.92	16.46	77.80	5.69	16.50
IIb	NCH_3	H	H	H	21.6[c]	163—164	EtOH	90	$C_{12}H_{12}N_2$	78.23	6.57	15.21	78.44	6.58	15.60
IVa	S	H	H	H	48.9	123—124[f]	EtOH	54.2	$C_{11}H_9NOS$	65.10	4.40	6.90	65.20	4.50	6.90
IVb	S	H	H	3-CH_3	47.0	83— 84	EtOH	25	$C_{12}H_{11}NOS$	66.33	5.10	6.51	66.20	4.84	6.51
IVc	S	7-Cl	H	3-CH_3	53.4	120—121	PrOH	76	$C_{12}H_{10}ClNOS$	57.26	4.00	5.56	57.12	3.74	5.57
IVd	S	H	C_6H_5	3-CH_3	*	204—208	EtOH	37	$C_{18}H_{15}NOS$	73.69	5.05	4.77	73.46	5.22	4.81
IVe	S	H	H	3,3-diMe	*	95— 96	*n*-C_6H_{14}	40	$C_{13}H_{13}NOS$	67.50	5.66	6.06	67.34	5.60	5.72
VIa	O	H	H	H	*	117—119	AcOEt	59.1	$C_{11}H_9NO_2$	70.58	4.85	7.48	70.89	4.80	7.51
VIb	O	7-Cl	H	H	*	138—139	EtOH	22	$C_{11}H_8ClNO_2$	59.61	3.64	6.14	59.37	3.56	6.14
VIc	O	H	C_6H_5	H	*	166—168	EtOH	63	$C_{17}H_{13}NO_2$	77.54	4.98	5.32	77.82	5.31	4.90
VId	O	H	H	3,3-diMe	27.8	91— 92	Cyclohexane	55	$C_{13}H_{13}NO_2$	72.54	6.09	6.51	72.21	6.03	6.65
VIIa	SO	H	H	H	41.2	160—162	EtOH	60	$C_{11}H_9NO_2S$	60.26	4.14	6.39	60.28	4.07	6.33
VIIb	SO	7-Cl	H	H	57.5	216—217	EtOH	58	$C_{11}H_8ClNO_2S$	52.08	3.18	5.52	51.82	3.04	5.43
VIIc	SO	7-Cl	H	3-CH_3	58.0	171—172	EtOH	47	$C_{12}H_{12}ClNO_2S$	53.83	3.76	5.23	53.85	4.01	4.87
VIId	SO	7-$N(CH_3)_2$	H	H	*	194—195	Benzene–*n*-C_6H_{14}	30	$C_{13}H_{14}N_2O_2S$	59.52	5.38	10.68	59.44	5.30	10.30
VIIIa	SO_2	H	H	H	38.1[d]	208—211	EtOH	48	$C_{11}H_9NO_3S$	56.16	3.87	5.95	56.04	3.66	5.85
VIIIb	SO_2	7-Cl	H	H	*	255—256	AcOH	69	$C_{11}H_8ClNO_3S$	48.99	2.99	5.19	48.73	2.94	5.14
VIIIc	SO_2	7-Cl	H	3-CH_3	*	226—227	AcOH	40	$C_{12}H_{14}ClNO_3S$	50.80	3.55	4.94	50.59	3.84	4.96



Compd. No.	Y	R_1	R_2	R_3	Antiinf. activity[a] (25 mg/kg)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIc	NCH_3	H	H	H	*	127—128[g]	iso-PrOH	70	$C_{13}H_{14}N_2O$	78.75	7.12	14.13	78.45	7.00	14.40
IVf	S	H	H	H	54.6	85— 86	EtOH	69	$C_{12}H_{11}NOS$	66.33	5.10	6.45	66.16	4.91	6.22
IVg	S	8-Cl	H	H	57.1	117—118	iso-PrOH	64.8	$C_{12}H_{10}ClNOS$	57.26	4.00	5.56	57.01	3.98	5.32
IVh	S	8-NO_2	H	H	*	224—226	AcOEt	20	$C_{12}H_{10}N_2O_3S$	54.95	3.84	10.68	54.60	3.93	10.50
IVi	S	8-NH_2	H	H	*	151—152	Benzene–*n*-C_6H_{14}	38.5	$C_{12}H_{12}N_2OS$	62.04	5.21	12.06	62.01	5.27	12.05
IVj	S	8-$NHCH_3$	H	H	*	171—172	Benzene–*n*-C_6H_{14}	11	$C_{13}H_{14}N_2OS$	63.39	5.27	12.05	63.28	5.75	12.27
IVk	S	8-$N(CH_3)_2$	H	H	*	141—142	Cyclohexane	15	$C_{14}H_{16}N_2OS$	64.59	6.19	10.76	64.44	4.61	10.61
IVl	S	8-OH	H	H	*	230—231	iso-PrOH	42	$C_{12}H_{11}NO_2S$	61.78	4.75	6.00	61.64	4.61	5.87
IVm	S	8-OCH_3	H	H	*	125—126	iso-PrOH	52.5	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	62.95	5.25	5.49
IVn	S	9-OCH_3	H	H	*	86— 87	iso-PrOH	55	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	63.08	5.25	5.71
IVo	S	10-OCH_3	H	H	*	117—118	iso-PrOH	43	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	63.07	5.26	5.57
IVp	S	8,9-OCH_2O–	H	H	49.1	121—122	iso-PrOH	87	$C_{13}H_{11}NO_3S$	59.76	4.24	5.36	59.39	4.40	5.07
IVq	S	7-OH	CH_3	H	*	110—112	iso-PrOH	67	$C_{13}H_{13}NO_2S$	63.14	5.30	5.66	62.89	5.29	5.81
IVr	S	7-OCH_3	CH_3	H	*	122—123	Cyclohexane	94	$C_{14}H_{15}NO_2S$	64.35	5.79	5.33	64.10	5.83	5.51
IVs	S	H	CH_3	H	31.1	96— 98	EtOH	64	$C_{13}H_{13}NOS$	67.50	5.66	6.06	67.13	5.73	5.75
IVt	S	H	$CH(CH_3)_2$	H	*	123—124	EtOH–H_2O	32	$C_{15}H_{17}NOS$	69.46	6.61	5.40	69.02	6.49	5.18
IVu	S	H	$CH_2C_6H_5$	H	*	234—235	EtOH	71	$C_{19}H_{17}NOS$	74.24	5.57	4.56	74.01	5.55	4.56
IVv	S	H	C_6H_5	H	*	166—168	EtOH	52	$C_{19}H_{14}NOS$	73.69	5.15	4.77	73.52	5.14	4.67
IVw[h]	S	9-Cl	H	H	51.4	109—110	iso-PrOH	40	$C_{12}H_{10}ClNOS$	57.26	4.00	5.56	57.11	3.89	5.35
IVx[h]	S	8-CH_3	H	H	20	89— 90	Cyclohexane	39.5	$C_{13}H_{13}NOS$	67.50	5.66	6.06	67.79	5.70	5.75
IVy[h]	S	7-Cl	H	H	28.1	79— 80	iso-PrOH	16	$C_{12}H_{10}ClNOS$	57.26	4.00	5.56	57.50	4.15	5.44

Compd. No.	Y	R_1	R_2	R_3	Antiinf. activity[a] (25 mg/kg)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIc	O	H	H	H	30.6[d]	100—101	EtOH	17	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	71.61	5.53	6.85
VId	O	8-Cl	H	H	*	115—116	EtOH	27	$C_{12}H_{16}ClNO_2$	61.66	4.28	5.94	61.52	4.16	5.94
VIIe	SO	H	H	H	55.3	132—133	EtOH	51	$C_{12}H_{11}NO_2S$	61.78	4.75	6.00	61.85	4.36	5.67
VIIf	SO	8-Cl	H	H	57.0	147—148	EtOH	71	$C_{12}H_{10}ClNO_2S$	53.83	3.76	5.32	53.61	3.70	4.99
VIIg	SO	8-$N(CH_3)_2$	H	H	*	190—192	Benzene–n-C_6H_{14}	51.5	$C_{14}H_{16}N_2OS$	60.85	5.84	10.14	61.09	5.88	9.55
VIIh	SO	8-OCH_3	H	H	*	188—189	EtOH	69	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	59.01	4.99	5.11
VIIi	SO	8,9-OCH_2O–	H	H	45.0	189—190	EtOH	62	$C_{13}H_{11}NO_4S$	56.31	4.00	5.05	56.69	3.89	4.62
VIIj	SO	H	$CH_2C_6H_5$	H	*	147—148	EtOH	57	$C_{19}H_{17}NO_2S$	70.56	5.30	4.33	70.27	5.38	4.12
VIIId	SO_2	H	H	H	46.7	206—208	EtOH	60	$C_{12}H_{10}NO_3S$	57.82	4.45	5.62	57.69	4.32	5.67
VIIIe	SO_2	8-Cl	H	H	*	234—235	AcOH	70	$C_{12}H_{10}ClNO_3S$	50.80	3.55	4.94	50.47	3.45	4.94
VIIIf	SO_2	8-NO_2	H	H	*	242—244	AcOH	50	$C_{12}H_{10}N_2O_5S$	54.95	3.84	10.68	54.60	3.69	10.50
VIIIg	SO_2	8-OCH_3	H	H	*	215—216	AcOH	61	$C_{13}H_{13}NO_4S$	55.94	4.69	5.01	55.52	4.66	4.92
VIIIh	SO_2	9-OCH_3	H	H	*	256—257	AcOH	64	$C_{13}H_{13}NO_4S$	55.94	4.69	5.01	55.76	4.63	4.89
VIIIi	SO_2	10-OCH_3	H	H	*	251—252	EtOH	75	$C_{13}H_{13}NO_4S$	55.94	4.69	5.01	55.76	4.57	5.22
VIIIj	SO_2	8,9-OCH_2O–	H	H	*	261—262	AcOH	17	$C_{13}H_{11}NO_5S$	53.24	3.78	4.78	52.83	3.76	4.82
VIIIk	SO_2	H	CH_3	H	45.7	186—188	AcOH	70	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	59.02	4.85	5.12
VIIIl	SO_2	8-CH_3	H	H	*	219—221	AcOEt	59	$C_{13}H_{13}NO_3S$	59.30	4.98	5.32	59.03	4.82	5.04
VIIIm	SO_2	9-Cl	H	H	33.9	209—211	AcOH	40	$C_{12}H_{10}ClNO_3S$	50.80	3.50	4.94	51.00	3.70	5.10
Phenylbutazone					29.4										
Mepirizole					19.6										

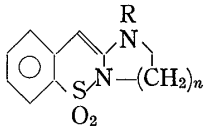
a) Antiinflamm atory activity; inhibition (%) of edema formation induced by carrageenin in the hind paw of the rat.
b) *: inhibition (%) of edema formation, less than 20%.
c) Ger patent 1951516, 163—164°.
d) Dose administered, 50 mg/kg (*p.o.*).
e) Lit., 3*a*, 216—217°.
f) Lit. 4, 123°.
g) Lit. 3*a*, 130—131°.
h) Compounds IVw—y were prepared from *o*-carboxyphenylmalonic acid derivatives instead of homophthalic acid derivatives following the procedure used for the synthesis of compound IVf.



XIIIa: $R_1=CH_3$
XIIIb: $R_1=C_2H_5$
XIIIc: $R_1=CH_2C_6H_5$

Chart 4

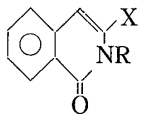
TABLE II.



Compd. No.	R	n	Antiinf. activity[a] (100 mg/kg)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
XIa	C_2H_5	1	42.0	123—124	MeOH	35	$C_{12}H_{14}N_2O_2S$	57.53 (57.34	5.64 5.66	11.19 11.08)
XIb	CH_3	1	28.8	157—158	MeOH	30	$C_{11}H_{12}N_2O_2S$	55.93 (55.64	5.08 5.02	11.86 11.90)
XIc	CH_3	2	24.1	160—161	MeOH	34.4	$C_{12}H_{14}N_2O_2S$	57.58 (57.61	5.64 5.65	11.19 11.30)
Phenylbutazone			51.2							

a) Antiinflammatory activity; inhibition (%) of edema formation induced by carrageenin in the hind paw of the rat.

TABLE III.



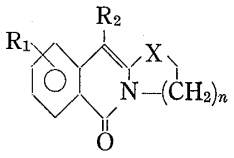
Compd. No.	X	R	Antiinf. activity[a] (50 mg/kg)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
XIIIa	SCH_2	CH_3	57.3	83— 85	Cyclohexane	71	$C_{11}H_{11}NOS$	64.36 (64.49	5.40 5.19	6.82 6.91)
XIIIb	SCH_2	C_2H_5	38.5	80— 82	Cyclohexane	49	$C_{12}H_{13}NOS$	65.42 (65.46	5.97 5.85	6.39 6.45)
XIIIc	SCH_3	$CH_2C_6H_5$	*[b]	79— 80	Cyclohexane	67.6	$C_{18}H_{17}NOS$	73.19 (73.39	5.80 5.80	4.74 4.38)
XIV	$SOCH_3$	CH_3	55.8	157—159	MeOH	65	$C_{11}H_{11}NO_2S$	59.71 (59.54	5.01 4.78	6.33 6.51)
XV	SO_2CH_3	CH_3	50.7	179—180	EtOH	52	$C_{11}H_{11}NO_3S$	55.68 (55.51	4.47 4.34	5.90 5.79)
Phenylbutazone			44.5							

a) Antiinflammatory activity; inhibition (%) of edema formation induced by carrageenin in the hind paw of the rat.
b) *: inhibition (%) of edema formation, less than 20%.

3-Alkylthio-substituted isoquinolones were also prepared. Reaction of 3-chloroisoquinolone[7] with dimethyl sulfate or an alkyl halides in the presence of sodium methoxide gave N-alkyl-3-chloroisoquinolones (XII). On treatment with an alkylthiolate, XII was converted to 3-alkylthio-substituted isoquinolones (XIII). Compound XIIIa was oxidized to the corresponding sulfoxide (XIV) and sulfone (XV). Data for these compounds are listed in Table III.

Pharmacology and Discussion

TABLE IV. Analgesic Activity[a]



Compd. No.	R_1	R_2	n	X	50 mg/kg
IIb	H	H	1	NCH_3	51.5
IIc	H	H	2	NCH_3	50.0
IVa	H	H	1	S	46.4
IVc	8-Cl	H	1	S	70.0
IVf	H	H	2	S	57.8
IVg	8-Cl	H	2	S	28.8
IVs	H	CH_3	2	S	31.6
IVw	9-Cl	H	2	S	25.0
VIa	H	H	1	O	90.7
VIIa	H	H	1	SO	39.7
VIIb	8-Cl	H	1	SO	74.3
VIIc	H	H	2	SO	58.6
VIIf	8-Cl	H	2	SO	61.6
VIIId	H	H	2	SO_2	14.4
VIIIk	H	CH_3	2	SO_2	44.4
Aminopyrine					58.1

a) Inhibition (%) of writhing induced by acetic acid in mice.

The anti-inflammatory activity of these compounds was determined by means of the carrageenin paw edema assay method as described by Winter, *et al.*[8] and was compared with that of phenylbutazone and mepirizole. The tricyclic compounds IVa, f, VIIa, c and VIIId, k showed stronger activity than phenylbutazone and mepirizole but XIa, c with a sulfonamide bond instead of the amide bond, showed only weak activity. The activity of alkylthio isoquinolones (XIII—XV) was rather weak compared with those of IVf and VIIId, k. Among the thiazino derivatives having a substituent on the benzene ring, halogen substituted compounds retained the activity, but their oxidation products VIIIb, c, m showed markedly decreased activity.

Compounds having a substituent larger than a methyl group at the 11-position of IVf did not show significant activity in our test system. Compounds showing relatively strong anti-inflammatory activity were selected and examined for analgesic activity in terms of the inhibition of writhing induced by acetic acid.[9]

Most of the compounds showed analgesic activity stronger than that of aminopyrine. These compounds were next tested for acute toxicity in mice (*p.o.*). The toxicity decreased in the order IV, VI and VIII. Among them, VIIId and VIIIk showed remarkably low

7) G. Simchen and G. Entenman, Angew. *Chem. Int. Ed. Engl.*, **12**, 2607 (1975).
8) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
9) R. Kostar, M. Anderson, and E.J. Debbeer, *Fed. Proc.*, **22**, 248 (1963).

toxicities and none of the mice tested died even after the oral administration of 2500 mg/kg. VIIIk showed an ED_{50} value of 33 mg/kg in the rat carrageenin paw edema assay method and an ED_{50} value of 55 mg/kg in the acetic acid induced writhing assay method. Thus VIIIk was selected for further study, and pharmacological data on this compound will be reported elsewhere.

Experimental[10]

6-Oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline (IVf) and N-γ-Mercaptopropylhomophthalimide (III)——A mixture of 3.6 g of homophthalic acid (I), 3.4 g of 3-aminopropanethiol hydrobromide and 3.28 g AcONa in 110 ml of AcOH was refluxed overnight. The solvent was then evaporated off *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with dilute alkali, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was passed through a column of silica gel and eluted with $CHCl_3$ to give two fractions. The first fraction gave 1.8 g (yield 32%) of yellow oil, III. *Anal.* Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.22; H, 5.36; N, 5.84. NMR ($CDCl_3$) ppm: 1.5 (1H, t, J=8 Hz), 1.96 (2H, m), 2.56 (2H, t of t, J=7 Hz, J=7 Hz), 4.10 (2H, t, J=7 Hz), 4.04 (2H, s).

The second fraction was evaporated down and recrystallized from ethanol to give 0.8 g (yield 18.5%) of VIf, mp 85—86°. *Anal.* Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.16; H, 4.91; N, 6.22. NMR ($CDCl_3$) ppm: 2.14—2.4 (2H, m), 3.1 (2H, t, J=7 Hz), 4.2 (2H, t, J=7 Hz), 6.5 (1H, s), 8.3—8.5 (1H, m).

N-γ-Mercaptopropylhomophthalimide (III)——A mixture of 1.8 g of I, 1.72 g of 3-aminopropanethiol hydrobromide and 0.82 g of AcONa in 20 ml of *o*-dichlorobenzene was heated at 140—150° for 2 hr while removing water by azeotropic distillation. After cooling, the mixture was poured into ice-water and then extracted with $CHCl_3$.

The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue obtained was passed through a column of silica gel and eluted with $CHCl_3$ to give 1.3 g (yield 76%) of III.

6-Oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline (IVf)——A mixture of 0.112 g of N-γ-mercaptopropylhomophthalimide and 0.172 g of *p*-toluenesulfonic acid in 4 ml of *o*-dichlorobenzene was heated for 0.5 hr at 120°. The reaction mixture was condensed *in vacuo*.

The residue was extracted with benzene and the extract was washed with water, dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was recrystallized from EtOH to yield 0.07 g (yield 68%) of IVf.

Compound (IV): 6-Oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline (IVf)——A mixture of 3.6 g of I, 3.6 g of 3-aminopropanethiol hydrobromide and 1.64 g of AcONa in 20 ml of *o*-dichlorobenzene was heated. The temperature of the reaction mixture was gradually increased and the resulting water was removed by azeotropic distillation. After the water had been distilled off, the reaction temperature was kept at 140—150° for 1 hr, then 3.6 g of *p*-toluenesulfonic acid was added at a temperature below 100°. After stirring for 1 hr, the reaction mixture was cooled at room temperature, poured into ice-water and extracted twice with $CHCl_3$. The combined extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from EtOH to yield 3.0 g of IVf (yield 69%). Compounds IVb—IVy were prepared in the same manner.

Compound VI: 5-Oxo-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinoline (VIa)——A mixture of 3.6 g of I, 1.2 g of 2-aminoethanol and 0.1 g of *p*-toluenesulfonic acid in 20 ml of *o*-dichlorobenzene was heated at 150—160° for 3 hr. The solvent was evaporated off *in vacuo* and the residue was recrystallized from AcOEt to give 2.2 g (yield 59.1%) of VIa, mp 117—119°.

MS *m/e*: 187 (M^+). *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.87; H, 4.80; N, 7.51. NMR ($CDCl_3$) ppm: 4.3 (2H, t, J=7 Hz), 4.64 (2H, t, J=7 Hz), 8.28 (1H, d, J=8 Hz), 5.86 (1H, s). Compounds VIb—VId were prepared in the same manner.

Compound VII: 6-Oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline-1-oxide (VIIe)——H_2O_2 (30%, 0.57 ml) was added dropwise to a solution of 1.65 g of IVf in 10 ml of AcOH. The reaction mixture was stirred overnight at room temperature and then poured into ice-water. The resulting precipitate was collected and recrystallized from EtOH to give 0.9 g of VIIe, mp 132—133°.

MS *m/e*: 233 (M^+). *Anal.* Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.85; H, 4.36; N, 5.67.

Compounds VIIa—VIIj were prepared in the same manner.

Compound VIII: 6-Oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline-1,1-dioxide (VIIId)——A solution of 1.5 g of IVf in 50 ml of AcOH was treated with 1.58 ml of 30% H_2O_2 and the mixture was kept at

10) All melting points are uncorrected. IR spectra were run on a Hitachi 215 spectrometer. NMR spectra were recorded at 100 MHz with a JEOL-MH100 or a JEOL-FX 100 machine using TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet. Mass spectra were obtained using a Hitachi RMU-6MG double-focusing mass spectrometer.

70—80° for 3 hr. The reaction mixture was cooled and the resulting precipitate was collected and recrystallized from AcOH to yield 1.17 g (yield 60%) of VIIId, mp 206—208°.

MS *m/e*: 249 (M^+). *Anal.* Calcd. for $C_{12}H_{11}NO_3S$; C, 57.82; H, 4.45; N, 5.62. Found: C, 57.69; H, 4.32; N, 5.69. NMR (DMSO-d_6) ppm: 2.3—2.6 (2H, m, C_3–H), 3.72 (2H, t, J=7 Hz, C_2–H), 4.27 (2H, t, J=7 Hz, C_4–H), 7.5 (1H, s, C_{11}–H). Compounds VIIIa—VIIIm were prepared in the same manner.

Compound XI: 1-Ethyl-2,3-dihydro-1H-imidazo[3,2-*b*](1,2)benzothiazine-5,5-dioxide (XIa)——A solution of 2.6 g of N-ethylethylenediamine in 30 ml of dry toluene was treated with 3.2 g of *o*-chlorosulfonyl benzylcyanide in 60 ml of dry toluene at −15° dropwise. The reaction mixture was stirred at room temperature for 4 days. The solvent was evaporated off and the residue was washed with ether then recrystallized from MeOH to give 1.4 g (yield 35%) of XIa, mp 123—124°. MS *m/e*: 250 (M^+). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.34; H, 5.66; N, 11.08. NMR ($CDCl_3$) ppm: 1.2 (3H, t, J=7 Hz), 3.2 (2H, q, J=7 Hz), 3.4 (2H, t, J=7 Hz), 4.0 (2H, t, J=7 Hz), 5.1 (1H, s), 7.0—7.4 (3H, m), 7.7—7.85 (1H, m). Compounds XIb and XIc were prepared in the same manner.

***o*-(N-Ethylaminoethylaminosulfonyl)benzylcyanide Hydrochloride (Xa)**——*o*-Chlorosulfonylbenzylcyanide (0.43 g) was added dropwise to a solution of 0.176 g of N-ethylethylenediamine in 10 ml of dry toluene at −15°. The reaction mixture was stirred at room temperature for 4 days. The solvent was evaporated off *in vacuo* and the residue was recrystallized from MeOH to give 0.35 g (yield 57.7%) of Xa, mp 149—151°. MS *m/e*: 267 (M^+). *Anal.* Calcd. for $C_{12}H_{18}ClN_3O_2S$: C, 47.44; H, 5.97; N, 13.83; Cl, 11.67. Found: C, 47.64; H, 6.06; N, 13.48; Cl, 11.56. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN). NMR (DMSO-d_6) ppm: 1.2 (3H, t, J=7 Hz), 2.8—3.2 (6H, m), 4.48 (2H, s), 7.6—7.8 (3H, m), 8.0 (1H, d, J=8 Hz), 8.64 (1H, broad) 9.0—9.4 (1H, broad).

1-Ethyl-2,3-dihydro-1H-imidazo[3,2-*b*](1,2)benzothiazine-5,5-dioxide (XIa)——Triethylamine (0.018 g) was added to a solution of 0.055 g of Xa in 1 ml of MeOH, and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated off *in vacuo* and the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from MeOH to give 0.02 g (yield 44%) of XIa.

Compound XIII: 2-Methyl-3-methylthioisoquinolone (XIIIa)——A mixture of 5.0 g of 3-chloro-2-methyl-1-oxo-1,2-dihydroisoquinoline and 7.5 g of 20% sodium methylsulfide in 20 ml of dimethylformamide was refluxed for 1.5 hr. The reaction mixture was cooled, poured into water and then extracted twice with AcOEt. The extract was washed with water and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* and the residue was recrystallized from cyclohexane to give 3.8 g (yield 71%) of XIIIa, mp 83—85°. *Anal.* Calcd. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.49; H, 5.17; N, 6.91. Compound XIIIb and XIIIc were prepared in the same manner.

The oxidation of XIIIa to give XIV and XV was performed as described for compounds VII and VIII.

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