Experimental Section

3-Piperidinocyclohexanone (X).—A mixt of cyclohexen-2-one (40 g), piperidine (130 ml), and H_2O (10 ml) was refluxed 1 hr and distd to give X (35 g, 49%), bp 101–102° (0.6 mm). It gave a **hydrobromide**, mp 179° (from *i*-PrOH–Et_2O). *Anal.* ($C_{11}H_{20}BrNO$) C, H, Br, N.

***cis*-(IIIa) and *trans*-(IIIb) 1-Phenyl-3-piperidinocyclohexan-1-ol.**—A soln of X (40 g) in Et_2O (200 ml) was added to PhLi [from Li (4.9 g) and PhBr (55 g)] in Et_2O (200 ml) and refluxed 1 hr. The cooled product was poured into H_2O and acidified with AcOH. The aq soln was washed (Et_2O), basified (NH_4OH), and extd with Et_2O (3x). The combined exts were dried ($MgSO_4$) and evapd. Several recrystns of the residue from petr ether (bp 80–100°) gave IIIb, 20 g (35%), mp 111–112°. *Anal.* ($C_{17}H_{25}NO$) C, H, N. It gave a **hydrochloride**, mp 254–255° (from EtOH–Et_2O). *Anal.* $C_{17}H_{26}ClNO$ C, H, Cl, N. Evap of the mother liquors and recrystn from petr ether (bp 40–60°) gave IIIa (9 g, 16%), mp 80°. *Anal.* C, H, N. It gave a **hydrochloride**, mp 247.5° (from EtOH–Et_2O). *Anal.* C, H, Cl, N

***cis*-1-Acetoxy-1-phenyl-3-piperidinocyclohexane (XI).**—A soln of IIIa (0.5 g) in pyridine (1.5 ml) and Ac_2O (1.5 ml) was refluxed 0.75 hr, the solvents were evapd, and the residue was treated with HCl gas to give XI·HCl (0.4 g, 61%), mp 195° (from EtOH–Et_2O). *Anal.* ($C_{19}H_{28}ClNO_2$) C, H, Cl, N.

***trans*-1-Acetoxy-1-phenyl-3-piperidinocyclohexane (XII).**—A soln of IIIb (1 g) in Et_2O (5 ml) was added to PhLi [from Li (0.08 g) and PhBr (0.9 g)] in Et_2O (15 ml) and refluxed 15 min. Ac_2O (1.2 g) was added dropwise with ice cooling and the mixt was allowed to warm to room temp with stirring overnight. Acid–base extn and treatment of the crude product with HCl gas gave XII·HCl (1.3 g 99%), mp 184–185° (from EtOH–Et_2O). *Anal.* C, H, Cl, N.

Ethyl (1-Methylamino)cyclohexylacetate (VI).—A soln of $MeNH_2$ (2.5 g) and V (4.5 g) in EtOH (10 ml) was allowed to stand overnight. Evap of excess $MeNH_2$ and treatment of the residue with HCl gas gave VI·HCl (3 g, 48%), mp 114–115° (from EtOAc). *Anal.* ($C_{11}H_{22}ClNO_2$) C, H, Cl, N.

Ethyl (1-Dimethylamino)cyclohexylacetate (VII).—Na_2CO_3 (3.2 g) was added to a soln of VI (5 g) and MeI (6.3 g) in EtOH (50 ml). The mixt was refluxed 1.5 hr. After acid–base extn the residue was treated with HCl gas to give VII·HCl (4.5 g 72%), mp 117° (from EtOAc). *Anal.* ($C_{12}H_{24}ClNO_2$) C, H, Cl, N.

1-Dimethylamino-1-(2,2-diphenyl-2-hydroxyethyl)cyclohexane (I).—A soln of VII (9.5 g) in Et_2O (100 ml) was added to PhLi [from Li (1.7 g) and PhBr (17.6 g)] in Et_2O (200 ml) and refluxed 2 hr. Acid–base extn gave I (4 g, 35%), mp 152–153° (from petr ether, bp 80–100°). *Anal.* ($C_{22}H_{29}NO$) C, H, N. It gave a hydrochloride, mp 197° (from *i*-PrOH–Et_2O). *Anal.* ($C_{22}H_{30}ClNO$) C, H, Cl, N.

***N*-Methyl-1-phenylcyclohexylamine, (VIII).**—A soln of VI (10 g) in Et_2O (50 ml) was added to PhLi [from Li (2.8 g) and PhBr (31.4 g)] and refluxed 12 hr. After acid–base extn, the product was treated with HCl gas to give VIII·HCl (6 g, 53%), mp 190–191° (from EtOAc). *Anal.* ($C_{13}H_{20}ClN$) C, H, Cl, N. It gave a picrolonate, mp 227° dec (from MeOH). *Anal.* ($C_{23}H_{27}N_5O_5$) C, H, N.

Acknowledgment.—I am indebted to Dr. D. Jack of Allen and Hanburys Ltd., Ware, Hertfordshire, for the pharmacological results.

Antiinflammatory 3,4-Dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxamide 1,1-Dioxides[1]

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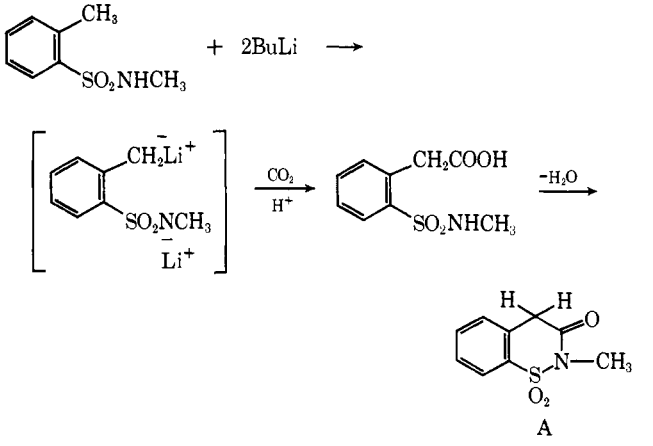
A general procedure for preparing 3,4-dihydro-2-alkyl-1,2-benzothiazine-3(2*H*)-one 1,1-dioxide has been found. A number of 4-carboxamides derived from this ring system are moderately acidic and exist as the diketo (nonenolized) form. These β-keto carboxamides exhibit potent antiinflammatory activity in the carrageenin-induced rat foot edema test. Such activity is also present in adrenalectomized rats. Activity as high as 1.5 times that of indomethacin was observed with some members of this family.

Previous publications have described the antiinflammatory activity of certain 2-methyl-1,3-dioxoisoquinoline-4-carboxanilides.[2] These results prompted the preparation of 3,4-dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxamide 1,1-dioxides. Preparation of 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide and the discovery of potent antiinflammatory activity for carboxamides derived from this heterocyclic system form the basis of this report.

Chemistry.—No examples of the 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide ring system were known when this work was initiated. One possible approach to such compounds was visualized by applying the lithiation technique of Gay and Hauser[3] to *N*-methyl-*o*-toluenesulfonamide. When this was done, both the sulfonamide N and the *o*-Me group were apparently lithiated since treatment of the resultant dilithio salt with CO_2 followed by a cyclodehydration produced the desired 3,4-dihydro-2-methyl-1,2-benzothiazine-3(2*H*)-one 1,1-dioxide (A). (Intermediate compds will hereafter be given letter designations while all carboxamides will be numbered.) This technique proved to be quite



A

general since *N*-benzyl-*o*-toluenesulfonamide gave 2-benzyl-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine 1,1-

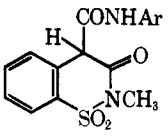
(1) Presented in part before the Medicinal Division at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971.

(2) (a) S. B. Kadin and E. H. Wiseman, *Nature (London)*, **222**, 275 (1969); (b) E. H. Wiseman, E. J. Gralla, J. Chiaini, J. R. Migliardi, and Y. H. Chang, *J. Pharm. Exp. Ther.*, **172**, 138 (1970).

(3) R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967).

TABLE I

3,4-DIHYDRO-2-METHYL-3-OXO-2*H*-1,2-BENZOTHIAZINE-4-CARBOXAMIDE 1,1-DIOXIDES



No.	Ar	Method of prepn[a]	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]	Anti-inflammatory activity[d]
1	C_6H_5[e]	a	52	154–156	E	$C_{16}H_{14}N_2O_4S$	2+
2	2-ClC_6H_4	a	74	139–141	B	$C_{16}H_{13}ClN_2O_4S$	2+
3	4-FC_6H_4	a	51	149–151	E	$C_{16}H_{13}FN_2O_4S$	3+
4	4-ClC_6H_4	a	61	148–150	E	$C_{16}H_{13}ClN_2O_4S$	2+
5	3-$CF_3C_6H_4$	a	38	136–138	E–W	$C_{17}H_{13}F_3N_2O_4S$	3+
6	4-$CH_3C_6H_4$	a	57	151–153	E	$C_{17}H_{16}N_2O_4S$	2+
7	4-$CH_3OC_6H_4$	a	75	165–167	E	$C_{17}H_{16}N_2O_5S$	2+
8	2,4-$Cl_2C_6H_3$[f]	a	58	206–208	A	$C_{16}H_{12}Cl_2N_2O_4S$	4+
9	4-BrC_6H_4[g]	a	42	165–167	E	$C_{16}H_{13}BrN_2O_4S$	5+
10	4-$NO_2C_6H_4$	a	22	209–212	A	$C_{16}H_{13}N_3O_6S$	5+
11	1-Naphthyl	a	54	197–199	A	$C_{20}H_{16}N_2O_4S$	+
12	3-$CH_3C_6H_4$	a	71	120–122	B	$C_{17}H_{16}N_2O_4S$	2+
13	4-$EtOC_6H_4$	a	72	162–164	E	$C_{18}H_{18}N_2O_5S$	−
14	3-ClC_6H_4	a	46	172–175	I	$C_{16}H_{13}ClN_2O_4S$	3+
15	2-$CH_3C_6H_4$	a	71	161–163	E	$C_{17}H_{16}N_2O_4S$	3+
16	2,5-$Cl_2C_6H_3$	a	37	184–186	B	$C_{16}H_{12}Cl_2N_2O_4S$	4+
17	2-$CH_3OC_6H_4$	a	67	157–159	E	$C_{17}H_{16}N_2O_5S$	2+
18	3,4-$Cl_2C_6H_3$	a	24	215–217	E	$C_{16}H_{12}Cl_2N_2O_4S$	2+
19	2-CH_3-4-$NO_2C_6H_3$[f]	a	35	206–209	A	$C_{17}H_{15}N_3O_6S$	5+
20	$CH_2CH{=}CH_2$	a	40	124–126	E	$C_{13}H_{14}N_2O_4S$	3+
21	COC_6H_5[h]	a	67	175–177	B	$C_{17}H_{14}N_2O_5S$	2+
22	4-$CF_3C_6H_4$[f]	a	6	147–149	I	$C_{17}H_{13}F_3N_2O_4S \cdot 0.5H_2O$	2+
23	4-$CH_3SO_2C_6H_4$[f]	a	22	178–180	E	$C_{17}H_{16}N_2O_6S_2$	+
24	4-$CH_3COC_6H_4$[f]	a	22	143–145	A	$C_{18}H_{16}N_2O_5S$	−
25	6-CH_3-2-pyridyl	b	12	218 dec	E	$C_{16}H_{15}N_3O_4S \cdot 0.5H_2O$	i
26	2-Pyridyl	b	24	205–207	E	$C_{15}H_{12}N_3O_4S \cdot 0.5H_2O$	−
27	2,4-$(CH_3O)_2C_6H_3$	b	25	174–176	E	$C_{18}H_{18}N_2O_6S$	+
28	4-$CH_3SC_6H_4$	b	48	192–194	E	$C_{17}H_{16}N_2O_4S_2$	+
29	3-Cl-4-$CH_3C_6H_3$	b	21	203–205	E	$C_{17}H_{15}ClN_2O_4S$	+
30	4-IC_6H_4	b	21	176–178	E	$C_{16}H_{13}IN_2O_4S$	4+
31	4-(*n*-C_4H_9)C_6H_4	b	30	173–175	E	$C_{20}H_{22}N_2O_4S$	3+
32	$CH_2C_6H_5$	b	25	147–149	E	$C_{17}H_{16}N_2O_4S$	4+
33	*n*-C_5H_{11}	b	24	108–110	X–H	$C_{15}H_{20}N_2O_4S$	3+
34	C_6H_{11}	b	32	178–180	E	$C_{16}H_{20}N_2O_4S$	3+
35	$CH_2CH_2C_6H_5$	b	35	188–190	E	$C_{18}H_{18}N_2O_4S$	+
	Indomethacin						5+

[a] Method a: prepd from 3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide (A) and the corresponding isocyanate as illustrated in the Experimental Section for 1. Method b: made from the corresponding amine and 3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-3-carboxylic acid, ethyl ester 1,1-dioxide (E) as illustrated for **28**. [b] E = EtOH; B = C_6H_6; W = H_2O; A = MeCN; I = *i*-PrOH; X = xylene; H = hexane; Et = ether; M = MeOH. [c] Satisfactory analyses for C, H, N were obtained for all of these compds. [d] Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals (6 rats/group) within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving aspirin (100 mg/kg po); +, drug given at 100 mg/kg; ++, drug given at 33 mg/kg; 3+, drug given at 10 mg/kg; 4+, drug given at 3.3 mg/kg; 5+, drug given at 1.0 mg/kg; po. Compds with antiinflammatory activity (at 100 mg/kg) of less than 0.5 times aspirin are reported as −; these latter compds, however, still exhibit low levels of inhibition of edema in this test. Similar results were obtained with **3**, **9**, and **19** in both adrenalectomized and nonadrenalectomized rats dosed at 33 mg/kg, po. [e] pK_a (2:1 dioxane–H_2O) = 5.98. [f] The requisite aryl isocyanate was synthesized from a substituted aniline and phosgene and used immediately (see Experimental Section). [g] pK_a = 5.63. A dose–response comparison of **9** with indomethacin at five dose levels indicated a potency ratio of 1.5. [h] The requisite C_6H_5CONCO, bp 97° (18 mm), was made according to A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963). [i] Inactive at 33 mg/kg; insufficient sample to test at 100 mg/kg.

dioxide (B) while 5-chloro-*N*-methyl- and *N*,5-dimethyl-*o*-toluenesulfonamide gave 7-chloro-2-methyl- and 2,7-dimethyl-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide (C and D), resp. Watanabe and Hauser[4a,b] have also described *o*-Me lithiation of *N*-alkyl-*o*-toluenesulfonamides which they then proceeded to react with various electrophiles. They did not, however, investigate the presently described carbonation of such dilithio salts.

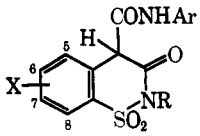
After completion of this work, Sianesi and coworkers[5] reported a 4-step procedure for preparing compds analogous to A. However, the ease of obtaining starting materials and the shorter reaction sequence would seem to recommend the present technique for preparing A.

(4) (a) H. Watanabe and C. R. Hauser, *J. Org. Chem.*, **33**, 4278 (1968); (b) H. Watanabe, C-L. Mao, I. T. Barnish, and C. R. Hauser, *ibid.*, **34**, 920 (1969).

(5) E. Sianesi, R. Redaelli, M. Bertani, and P. DaRe, *Chem. Ber.*, **103**, 1992 (1970).

TABLE II

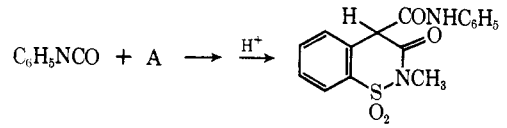
3,4-DIHYDRO-2-ALKYL-3-OXO-2*H*-1,2-BENZOTHIAZINE-4-CARBOXAMIDE 1,1-DIOXIDES[a]



No.	X	R	Ar	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]	Anti-inflammatory activity[d]
36	H	$CH_2C_6H_5$	C_6H_5	50	174–176	I	$C_{22}H_{18}N_2O_4S$	–
37	H	$CH_2C_6H_5$	4-ClC_6H_4	60	176–178	E	$C_{22}H_{17}ClN_2O_4S$	–
38	H	H	C_6H_5[e]	48	263–265	I–M	$C_{15}H_{12}N_2O_4S$	–
39	7-CH_3	CH_3	C_6H_5	69	176–178	I	$C_{17}H_{16}N_2O_4S$	2+
40	7-CH_3	CH_3	4-BrC_6H_4	33	166–168	Et–H	$C_{17}H_{15}BrN_2O_4S$	4+
41	7-CH_3	CH_3	4-$NO_2C_6H_4$	61	249–252	A	$C_{17}H_{15}N_3O_6S$	–
42	7-CH_3	CH_3	4-$CH_3OC_6H_4$	57	164–166	E	$C_{18}H_{18}N_2O_5S$	2+
43	7-CH_3	CH_3	2,4-$Cl_2C_6H_3$	39	160–163	A	$C_{17}H_{14}Cl_2N_2O_4S$	3+
44	7-Cl	CH_3	C_6H_5[f]	68	172–174	E	$C_{16}H_{13}ClN_2O_4S$	+
45	7-Cl	CH_3	4-BrC_6H_4	37	159–162	I–W	$C_{16}H_{12}ClBrN_2O_4S$	+
46	7-Cl	CH_3	2,4-$Cl_2C_6H_3$	38	183–186	B	$C_{16}H_{11}Cl_3N_2O_4S$	+

[a] Prepared from the appropriate 2,7-disubstituted-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide and an aryl isocyanate by the method used for 1 (method a). [b] See footnote *b* of Table I. [c] See footnote *c* of Table I. [d] See footnote *d* of Table I. [e] See Experimental Section. [f] pK_a (2:1 dioxane–H_2O) = 5.1.

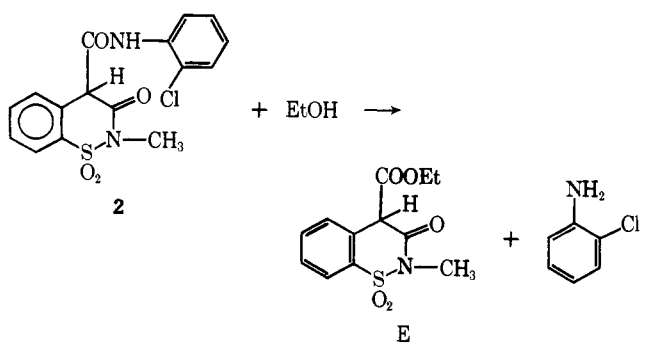
Upon treatment with phenyl isocyanate in DMSO in the presence of Et_3N, A was converted to the desired 4-carboxanilide (**1**).



1

Compd **1** proved to be an acid of moderate strength (pK_a = 5.98 in 2:1 dioxane–H_2O) and formed the basis for the synthesis of a large number of carboxamides summarized in Table I (method a) and Table II. Spectral evidence indicates that these compds exist as the keto (nonenolized) form, although all give a deep purple color with $FeCl_3$.

Since certain carboxamides analogous to **1** could not be made by the above mentioned route due to the difficulty in obtaining the requisite isocyanates, the ester E was made by the novel ethanolysis technique previously reported by Kadin.[6] Thus, 2′-chloro-3,4-dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxanilide 1,1-dioxide (**2**) was refluxed in EtOH to displace *o*-chloroaniline and produce the ester E. Ester E reacted with various amines in xylene soln to form the desired 4-carboxamides, usually in low yields (Table I, method b).



2 **E**

Pharmacology.—Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (Charles River Strain, average wt 170 g, 6 rats/group) in response to a subplantar injection of carrageenin. The experimental procedure followed that of Winter, *et al.*[7] Edema formation was measured 3 hr after oral administration of test drug (in aq soln), and the response of drug-treated animals was compared with that of controls, some receiving vehicle alone and others receiving aspirin (100 mg/kg).

Bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were maintained under light Et_2O anesthesia. Animals were maintained on a normal diet with 0.9% saline in place of drinking water, and were used 5–7 days postoperatively.

Discussion

Table I summarizes the antiinflammatory activities of the title compds. A dose–response comparison of **9** with indomethacin at 5 dose levels indicated **9** to be 1.5 times as potent as indomethacin. Compds **3**, **9**, and **29**, chosen as representatives of the family, exhibit similar antiinflammatory activities in either normal or adrenalectomized rats dosed at 33 mg/kg, po. Almost all of the more potent analogs (rated 4+ or higher) possess substituents with positive Hammet σ values in the 4 position of the anilide ring. Thus, **8**, **9**, **10**, **19**, and **30** have either a 4-halogen or 4-nitro function in the carboxanilide moiety. Compd **32**, however, is not an anilide, and **16** does not have a 4 substituent. Furthermore, 4-acetyl (**24**), 4-CF_3 (**22**), or 4-CH_3SO_2 (**23**) substituents did not produce superior activity. Thus, there is no obvious correlation between substitution on the carboxanilide ring and antiflammatory activity in this family of compounds.

(6) S. B. Kadin, *J. Org. Chem.*, **34**, 3178 (1969).

(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962); *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).

Experimental Section[8]

Most of the required isocyanates are commercially available and were used as received. Both *p*-bromo and *p*-nitrophenyl isocyanate were conveniently purified by ether trituration, filtration, and rapid evapn (*in vacuo*) of the filtrate to a solid which was used immediately. The required amines were purchased from Aldrich Chemical Co. Where necessary (see Table I, footnote *f*), aryl isocyanates were prepared using $COCl_2$ and the appropriate substituted aniline by the procedure previously reported[9] for *p*-trifluoromethylphenyl isocyanate. Isocyanates prepared for the first time include 2-methyl-4-nitrophenyl isocyanate (mp 79–82°), 4-methylsulfonylphenyl isocyanate (mp 94–97°), and 4-acetylphenyl isocyanate (mp 33–36°). These highly reactive isocyanates were not characterized further but were used immediately for the prepn (by method a) of the carboxanilides **19**, **23**, and **24**, resp.

Intermediates. 2-(*N*-Methylsulfamoyl)phenylacetic Acid.—To a soln of 31.4 g (0.17 mole) of *N*-methyl-*o*-toluenesulfonamide (mp 72–74°)[10] in 600 ml of dry THF at 0° was rapidly added 219 ml of 1.6 *M* BuLi in hexane. The orange-red soln was stirred at room temp for 15 min and then poured slowly onto a slurry of solid CO_2 in 1500 ml of Et_2O. After 1 hr, 500 ml of H_2O and 100 ml of 12 *N* HCl were added, and the soln was concd (*in vacuo*) to 700 ml. Cooling produced 29.1 g (75%) of white solid; mp 158–164° dec; ir (KBr) 3.0 (OH, NH), 5.83 (C=O), 7.52 and 8.62 (SO_2); sol in dil $NaHCO_3$. *Anal.* ($C_9H_{11}NO_4S$) C, H, N.

3,4-Dihydro-2-methyl-1,2-benzothiazine-3(2*H*)-one 1,1-Dioxide (A).—A soln of 29.0 g (0.13 mole) of 2-(*N*-methylsulfamoyl)-phenylacetic acid and 100 mg of *p*-TsOH in 1500 ml of dry xylene was refluxed for 18 hr under a Dean–Stark trap. Filtration and evapn of the filtrate (*in vacuo*) gave an oil which on crystn from IPO–H_2O gave A: 22 g (61%); mp 92–95°; insol in $NaHCO_3$, sol in NaOH; ir (KBr) 5.81 (C=O), 7.45 and 8.48 (SO_2); nmr ($CDCl_3$) τ 2.1 (m, 4, arom protons), 5.78 (s, 2, exchange in D_2O, CH_2), 6.83 (s, 3, NCH_3). *Anal.* ($C_9H_9NO_3S$) C, H, N.

***N*-Benzyl-*o*-toluenesulfonamide.**—Treatment of *o*-TsCl (K and K Laboratories) in PhH with excess $PhCH_2NH_2$ gave, after H_2O-washing, drying, and evapg the PhH layer, a mixt of *o*- and *p*-sulfonamides. The para isomer (mp 111–113°) was fractionally crystd first from EtOH and then from IPO. Evapn of the IPO filtrate to dryness gave 21% of nearly pure product, as a waxy solid, mp 44–47°. *Anal.* ($C_{14}H_{15}NO_2S$) C, H, N.

2-(*N*-Benzylsulfamoyl)phenylacetic Acid.—A soln of 26.2 g (0.10 mole) of *N*-benzyl-*o*-toluenesulfonamide in 500 ml of dry THF at 0° was treated with 156 ml of 1.6 *M* BuLi in hexane. After 20 min at room temp, the red soln was poured onto a slurry of solid CO_2 in 1500 ml of Et_2O. After 2 hr, 500 ml of H_2O and 100 ml of 12 *N* HCl were added, and the soln was concd *in vacuo* to 700 ml. Extn with $CHCl_3$, drying ($CaSO_4$), and evapn yielded an oil which was crystd from PhH: mp 107–109°; ir (KBr) 2.99 (NH, OH), 5.85 (C=O), 7.50 and 8.64 (SO_2). *Anal.* ($C_{15}H_{15}NO_4S$) C, H, N.

2-Benzyl-3,4-dihydro-1,2-benzothiazine-3(2*H*)-one 1,1-Dioxide (B).—2-(*N*-Benzylsulfamoyl)phenylacetic acid (0.5 g, 0.0016 mole) was pyrolyzed (under N_2) at 195° for 1 hr. Crystn of the dark residue (EtOH) gave 0.249 g (51%) of needles: mp 152–155°; ir (KBr) 5.86 (C=O), 7.40 and 8.46 (SO_2); nmr (DMSO-d_6), τ 1.8–2.5 (m, 4, arom protons), 2.69 (s, 5, C_6H_5), 5.02 (s, 2, $CH_2C_6H_5$), 5.70 (s, 2, CH_2, exchange in D_2O). *Anal.* ($C_{15}H_{13}NO_3S$) C, H, N.

5-Chloro-*N*,2-dimethylbenzenesulfonamide.—This amide was prepd from 5-chloro-2-methylbenzenesulfonyl chloride[11] and excess 40% aq $MeNH_2$ in EtOH. The product, mp 96–98° after recrystn from IPO–H_2O, was obtained in 72% yield. *Anal.* ($C_8H_{10}ClNO_2S$) C, H, N.

4-Chloro-*N*-methyl-2-sulfamoylphenylacetic Acid.—A soln of 33.0 g (0.15 mole) of 5-chloro-*N*,2-dimethylbenzenesulfonamide in 500 ml of THF at −60° was treated with 200 ml of 1.6 *M* BuLi in hexane. The resulting red soln was stirred 1 hr at −60° after which 70 g of solid CO_2 was added. After the addn of 300 ml of H_2O and excess 6 *N* HCl, the yellow soln was concd *in vacuo* and extd with $CHCl_3$. After drying (Na_2SO_4), the exts yielded an oil which crystd from PhH, 9.1 g (23%), mp 143–145°. *Anal.* ($C_9H_{10}ClNO_4S$) C, H, N.

7-Chloro-3,4-dihydro-2-methyl-1,2-benzothiazin-3(2*H*)-one 1,1-Dioxide (C).—A soln of 8.0 g (0.030 mole) of 4-chloro-*N*-methyl-2-sulfamoylphenylacetic acid and 100 mg of *p*-TsOH in 500 ml of dry PhMe was refluxed for 1 hr under a Dean–Stark trap. After filtration, evapn to dryness, and crystn from IPO, there was obtd 6.0 g (81%) of compd C, mp 123–125°. *Anal.* ($C_9H_8ClNO_3S$) C, H, N.

3,4-Dihydro-2,7-dimethyl-1,2-benzothiazin-3(2*H*)-one 1,1-Dioxide (D).—*N*-2,5-Trimethylbenzenesulfonamide was prepd in 93% yield from 2,5-dimethylbenzenesulfonyl chloride (Eastman Organic Chemicals) and excess 40% $MeNH_2$, mp 91–92° after recrystn from EtOH. To 33.9 g (0.17 mole) of this sulfonamide in 600 ml of THF at 0° was add 219 ml of 1.6 *M* BuLi in hexane. After 0.5 hr at room temp, the red soln was poured onto a slurry of solid CO_2 in 1500 ml of Et_2O. After adding 500 ml of H_2O and 100 ml of 12 *N* HCl, concn (*in vacuo*) to 800 ml gave white crystals, mp 146–151°, presumably *N*,4-dimethyl-2-sulfamoylphenylacetic acid. All of this crude carboxylic acid was cyclized to D in refluxing PhMe (2 hr, Dean–Stark trap) in the presence of 100 mg of *p*-TsOH. After removal of PhMe, recrystn from IPO gave 51% of D, mp 91–93. *Anal.* ($C_{10}H_{11}NO_3S$) C, H, N.

2-Methyl-1,2-benzothiazin-3(2*H*)-one-4-carboxylic Acid Ethyl Ester 1,1-Dioxide (E).—A soln of 4.0 g (0.011 mole) of the *o*-chlorocarboxanilide **2** in 75 ml of abs EtOH was refluxed for 24 hr. After removal of all solvent *in vacuo*, the residual oil was dissolved in Et_2O and washed with 6 *N* HCl (twice), then with H_2O (twice). After drying ($CaSO_4$), evapn of the Et_2O layer gave 1.9 g (61%) of a soft solid which was further purified by an Et_2O–hexane trituration, to give E; mp 68–70°; ir ($CHCl_3$) 5.70 (ester C=O), 5.82 (ring C=O), 7.35 and 8.50 (SO_2); mass spectrum *m/e* 283 (calcd 283) and 211 (loss of C≡O, CH_3CHO). $FeCl_3$ soln produces a purple color with E. *Anal.* ($C_{12}H_{13}NO_5S$) C, H, N.

Carboxamides. 3,4-Dihydro-2-methyl-3-oxo-2*H*-1,2-benzothiazine-4-carboxanilide 1,1-Dioxide (1) (Method a).—A soln of 1.1 g (0.005 mole) of 3,4-dihydro-2-methyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (A), 0.51 g (0.005 mole) of Et_3N, and 0.60 g (0.005 mole) of phenyl isocyanate in 10 ml of dry DMSO was stirred under N_2 for 24 hr at room temp. After pouring into 75 ml of 3 *N* HCl, the resulting yellow solid was recrystd from EtOH to give 0.85 g (52%) of **1**, mp 154–156°; $FeCl_3$ soln produces a deep purple color with **1**. Insol in dil $NaHCO_3$ but sol in dil NaOH: ir (KBr) 3.0 (NH), 5.80 (ring C=O), 5.99 (carboxanilide C=O), 7.40 and 8.45 (SO_2); nmr (DMSO-d_6) τ − 0.56 (s, 1, exchanges in D_2O, NH), 1.6–2.8 (m, 9, arom protons), 4.65 (s, 1, exchanges in D_2O, the 4 H), 6.76 (s, 3, NCH_3); pK_a = 5.98 (2:1 dioxane–H_2O), neut equiv 329 (calcd 330). See Tables I and II for analytical data on **1** and other carboxamides made by method a.

3,4-Dihydro-2-methyl-4′-methylthio-3-oxo-2*H*-1,2-benzothiazine-4-carboxanilide 1,1-Dioxide (28) (Method b).—A soln of 4.0 g (0.014 mole) of 2-methyl-1,2-benzothiazin-3(2*H*)-one-4-carboxylic acid ethyl ester 1,1-dioxide (E) and 2.1 g (0.015 mole) of 4-methylthioaniline in 250 ml of dry xylene under thoroughly dry N_2 was refluxed for 20 hr. During this period, the reflux condenser was periodically removed to allow approx 25-ml portions of solvent to boil off. After this time, evapn to dryness (*in vacuo*) and recrystn from EtOH gave 2.5 g (48%) of **28**, mp 189–192°. Another recrystn from EtOH gave anal. pure material: mp 192–194°; ir (KBr) 2.98 (NH), 5.77 (ring C=O), 5.95 (carboxanilide C=O), 7.40 and 8.46 (SO_2); **28** gives a purple color with dil $FeCl_3$. See Table I for anal. data on **28** and other carboxamides made by method b.

3,4-Dihydro-3-oxo-2*H*-1,2-benzothiazine-4-carboxanilide 1,1-Dioxide (38).—A suspension of 0.75 g (0.0019 mole) of 2-benzyl-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine-4-carboxanilide 1,1-dioxide (**36**) and 0.50 g of 10% Pd/C in 75 ml of MeOH was stirred under H_2. The theor vol of H_2 (45 ml) was taken up within 15 min. Filtration, evapn, and recrystn of the residue

(8) Melting points were determined in a Thomas-Hoover capillary melting point apparatus using a calibrated thermometer and are uncorrected. Potentiometric titrations were carried out in 2:1 dioxane–H_2O (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH; the apparent pK_a values correspond to the pH values at the half-neutralization point in these titrations. Ir spectra were determined in KBr pellets. Analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values. A Varian A-60 spectrometer (Me_4Si), was used to measure nmr spectra and mass spectra were detd on a Hitachi Perkin-Elmer Model RMU-6E.

(9) J. G. Lombardino and C. F. Gerber, *J. Med. Chem.*, **7**, 97 (1964).

(10) Prepared from *o*-toluenesulfonyl chloride and methylamine and recrystallized several times from C_6H_6–hexane. F. E. Clark, *Amer. Chem. J.*, **30**, 277 (1903), reports mp 74–75°.

(11) E. H. Huntress and F. H. Carten, *J. Amer. Chem. Soc.*, **62**, 511 (1940).

from IPO–MeOH gave 0.289 (48%) of anal. pure **38**, mp 263–265°. Anal. data are included in Table II.

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Phenacylthioimidazolines and 3-Aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles with Antidepressant Activity

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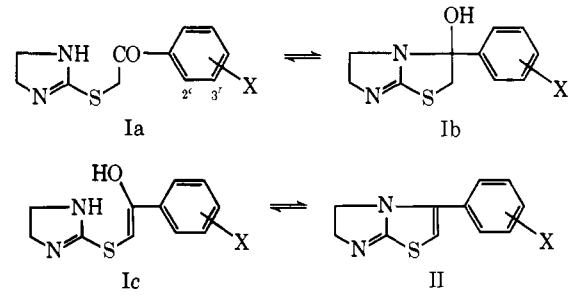
Some Ph-ring-substituted phenacylthioimidazolines are very potent antagonists of reserpine-induced hypothermia in mice. The proportion of open chain to cyclic carbinolamine tautomer depends on the type of substituent and possibly affects the activity. The 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles obtained by cyclodehydration are also active.

The reported antidepressant activity of 2-(3,4-dichlorophenoxymethyl)imidazoline[1] and an interest in imidazo[2,1-*b*]thiazoles, prompted us to prepare 2-(3,4-dichlorophenacylthio)imidazoline which proved to be exceptionally potent (ED_{50} = 0.5 mg/kg) in the reserpine hypothermia test in mice. The effects on antireserpine activity of substitution in the Ph ring of phenacylthioimidazoline and the activity of the corresponding 5,6-dihydroimidazo[2,1-*b*]thiazoles obtained by cyclodehydration were investigated. A patent[2] describing some related compounds with antidepressant properties has become available since this work was started.



inhibitor of MAO and no anorectic, analgetic, analeptic, or CNS-depressant properties were found. The acute

TABLE I

^{1}H Nmr Results (τ) for ArCOC(R^1R^2)S(HN–CH=N)

Ar	R^1	R^2	Aromatic protons[a,b]	$-CH_2CO$[b,c]	CH_2CH_2[a] $+CH_2C(Ar)OH$	Others	% keto form
4-$MeOC_6H_4$ (HBr)	H	H	1.77–3.05 (4)	4.70 (1)	5.53–6.50	6.05, 6.08 (MeO)	50
4-MeC_6H_4 (HBr)	H	H	1.88–2.83 (4)	4.73 (0.8)	5.50–6.83	7.68, 7.62 (Me)	40
C_6H_5 (HBr)	H	H	1.67–2.62 (5)	4.62 (0.54)	5.28–6.62		27
C_6H_5 (base)	H	H	2.27–2.80 (5)		5.83–7.27		0
3-ClC_6H_4 (HBr)	H	H	1.72–2.58 (4)	4.63 (0.5)	5.37–6.62		23
4-BrC_6H_4 (HBr)	H	H	1.97–2.55 (4)	4.72 (0.42)	5.45–6.63		21
4-ClC_6H_4 (HBr)	H	H	2.17–2.58 (4)	4.63 (0.3)	5.38–6.67		15
4-$NO_2C_6H_4$ (HBr)	H	H	2.33–2.98 (4)	4.58 (0.07)	5.20–6.63		3
C_6H_5 (HBr)	Me	H	2.18–2.62 (5)		5.33–6.57	8.62[d] (Me)	0
C_6H_5 (HBr)	Me	Me	2.17–2.55 (5)		5.45–6.33	8.38, 8.81 (Me)	0

[a] Multiplet. [b] Number of protons is given in parentheses. [c] Singlet. [d] Doublet. J = 7 Hz.

The most potent member of the series in the reserpine hypothermia test was **11** (I, X = 3′,4′-Cl_2, ED_{50} = 0.5 mg/kg), and its pharmacology was investigated in some detail. The results suggest strong antidepressant activity with some stimulant properties at higher dose levels. The antidepressant properties were similar in several respects to those of imipramine, but the anticholinergic activity was weak. Compd **11** was not an oral toxicity was low and a 30-day subchronic toxicity test in rats showed no major ill effects. A preliminary teratogenic study in rats and rabbits was also negative.

The results shown in Tables III and IV indicate that monosubstitution in the 3′ or 4′ position of I with either electron-attracting or electron-donating groups usually gave compds which were more active than the unsubstituted compd (I, X = H, **7**), but the most active ones (ED_{50} < 5 mg/kg) had electronegative substituents. Their activities, however, are not in the order of the Hammett σ constants and the high activity of the

(1) C-P Chien and R. M. Kaplan, *Curr. Ther. Res. Clin. Exp.*, **11**, 471 (1969).

(2) Sandoz AG, German Patents 1,924,769; 1,938,674 (1970).