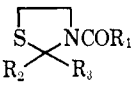
TABLE II



No.	R_1	R_2	R_3	Mp, C°	Crystn solvent	Formula[b]
1	3-Py[c]	H	H	194–196[a]	EtOH	$C_{15}H_{13}N_5O_3S$[a]
2	3-Py	Me	Et	170–172[a]	EtOH	$C_{18}H_{19}N_5O_3S$[a]
3	3-Py	Et	Et	183–184[a]	EtOH	$C_{19}H_{21}N_5O_3S$[a]
4	3-Py	H	*n*-Pr	134–136[a]	EtOH	$C_{18}H_{19}N_5O_3S$[a]
5	3-Py	H	$CH_3(CH_2)_6$	159–161[a]	EtOH	$C_{22}H_{27}N_5O_3S$[a]
6	3-Py	H	C_6H_5	99–100	EtOH	$C_{15}H_{14}N_2OS$
7	3-Py	H	4-ClC_6H_4	192–193[a]	EtOH	$C_{21}H_{16}ClN_5O_3S$[a,d]
8	3-Py	H	4-$CH_3OC_6H_4$	130–134[a]	EtOH	$C_{22}H_{19}N_5O_4S$[a]
9	$CH_3(CH_2)_3$	H	C_6H_5	68–69	Ligroin	$C_{14}H_{19}NOS$
10	$(CH_3)_2CHCH_2$	H	C_6H_5	64–65	Ligroin	$C_{14}H_{19}NOS$
11	$CH_3(CH_2)_{10}$	H	C_6H_5	55–56	EtOH–H_2O	$C_{21}H_{33}NOS$

[a] As picrate. [b] Elemental analyses were performed by A. Bernhardt, West Germany. The analytical results were within ±0.4% of the theoretical values. All compounds were analyzed for C, H, N, S. [c] Py = pyridyl. [d] Cl anal. also.

thiazolidines in Table I were unstable and too toxic for pharmacological test. None of the thiazolidines described in Table II showed significant activity in mice kept on a hyperlipidic diet in comparison with choline.

Experimental Section

All melting points were obtained in open capillary tubes and are uncorrected.

General Procedure for Compounds in Table I.—The 3-dimethylaminoacetylthiazolidines were prepared according to the literature[2a] and were converted into quaternary salts by treating their ethereal soln with an equimolar amount of MeI for 12 hr at room temp. The ppt was washed with Et_2O, dried *in vacuo*, and immediately analyzed for I^-.

General Procedure for Compounds in Table II.—The thiazolidines used for acylation were known products; they were synthesized according to described methods.[2a,b] The nicotinyl derivatives were prepared by adding nicotinyl chloride·HCl (0.02 mole) portionwise to a soln of the appropriate thiazolidine (0.02 mole) and Et_3N (0.04 mol) in CH_2Cl_2 (100 ml). After 20 hr at room temp the soln was concentrated *in vacuo* to dryness and washed (H_2O); the residue was dissolved in EtOH and purified by dilution (H_2O) and the sepd oil was crystd as the picrate in the usual way (EtOH).

For the preparation of the other acyl derivatives, Et_2O, and K_2CO_3 were used instead of CH_2Cl_2 and Et_3N, respectively.

Acknowledgment.—We thank Mr. A. Clerico for helpful assistance in synthetic work.

(2) (a) R. Tondeur, R. Sion and E. Deray, *Bull Soc. Chim. Fr.*, 2493 (1964). (b) E. D. Bergmann and A. Kaluszyner, *Recl. Trav. Chim. Pays-Bas*, **78**, 289 (1959).

Some Amides of 2-Hydroxy- (or Alkoxy-) 3-methoxybenzoic Acid

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The fact that amides of vanillic acid and their derivatives show various biological activities, notably analeptic,[1-3] antibacterial, and antifungal,[4] prompted us to perform the synthesis and pharmacological evaluation of the title amides. The standard methods of synthesis are given in the Experimental Section.

All of the amides listed in Table I were tested for antibacterial and antifungal actions,[5] and some of them were examined for CNS activity in mice,[6-8] for anti-inflammatory activity in rats and guinea pigs,[9-12] and analeptic activity in mice and rats.[13-15] None of the compounds in these tests showed anything worthy of note.

Experimental Section[16]

Amides were purified by recrystn or distn under reduced pressure. The 2-alkoxy- (methoxy-, ethoxy-, or isopropoxy-) 3-methoxy benzoic acids and their corresponding chlorides were prepared as reported previously.[17] 2-Acetoxy-3-methoxybenzoyl chloride was obtained in 88% yield, by treating the corresponding acid with $SOCl_2$. Low yields (25–30%) were encountered when 2-hydroxy-3-methoxybenzoyl chloride was prepared by refluxing *o*-vanillic acid with excess $SOCl_2$ in C_6H_6 for 1.5 hr.[18]

Amides of 2-Alkoxy-3-methoxybenzoic Acid.—A soln of the 2-alkoxy-3-methoxybenzoyl chloride (0.05 mole) in 20 ml of anhyd Et_2O was added dropwise with vigorous stirring to a soln of the amine (0.05 mole) in 40 ml of 1 *N* NaOH. Stirring was continued 30 min after completion of the addition. The mixture was extd with Et_2O. The combined exts were dried (Na_2SO_4) and evapd (see Table I).

2-Hydroxy-3-methoxybenzamides.—To a cooled soln of 2-acetoxy-3-methoxybenzoyl chloride (0.05 mole) in 50 ml of dry C_6H_6 was added dropwise with stirring a soln of amine (0.05 mole) and Et_3N (0.05 mole) in 30 ml of dry C_6H_6. Stirring was

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(1) K. Kratzl and E. Kvasnicka, *Monatsh. Chem.*, **83**, 18 (1952).

(2) K. Kratzl, K. H. Ginzel, E. Kvasnicka and M. Nelböck-Hochsteher, *Proc. Int. Congr. Biochem., 2nd*, **1952**, 437 (1953).

(3) B. Botta, L. Canonica, and E. Pavanati, *Atti. Soc. Lomb. Sci. Med. Biol.*, **9**, 22 (1954).

(4) I. A. Pearl and D. L. Beyer, *J. Amer. Chem. Soc.*, **75**, 2627 (1953).

(5) G. Coppi, A. Maselli, and C. Ciani-Bonardi, *Farmaco Ed. Sci.*, **20**, 203 (1965).

(6) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **93**, 470 (1948).

(7) J. R. Boissier, *Actual. Pharmacol.*, **12**, 7 (1959).

(8) C. Bianchi, *Arch. Int. Pharmacodyn. Ther.*, **111**, 227 (1957).

(9) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(10) L. O. Randall and J. T. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).

(11) J. Reinhart and E. de Beer in "Biological Standardization," J. Burn, D. Finney, and L. Goodwin, Ed., 2nd ed, Oxford University Press, London, 1950, p 316.

(12) E. Adami and E. Marazzi, *Arch. Int. Pharmacodyn. Ther.*, **107**, 322 (1956).

(13) P. Siegmund and M. Wolf, *Arch. Exp. Pathol. Pharmakol.*, **216**, 323 (1952).

(14) G. Chen and B. Bohner, *J. Pharmacol. Exp. Ther.*, **131**, 179 (1961).

(15) R. Rushton and H. Steinberg, *Nature (London)*, **197**, 1017 (1963).

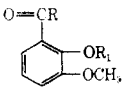
(16) Melting points and boiling points are not corrected.

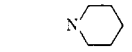
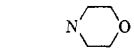
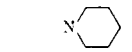
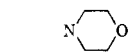
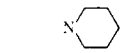
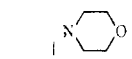
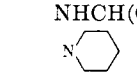
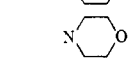
(17) G. Tsatsas and E. Costakis, *J. Med. Chem.*, **12**, 870 (1969).

(18) M. A. El-F. Ibrahim, H. A. El-Mangouri, aud Y. M. Abou-Zeid, *Congr. Sci. Farm. Conf. Comun., 21st*, **1961**, 468 (1962).

TABLE I

AMIDES OF 2-HYDROXY- (OR ALKOXY-) 3-METHOXYBENZOIC ACID



No.	R	R_1	Formula[a]	Mp or bp, (mm) °C	Yield,[c] %	Recrystn[d] solvent
1	NH_2	CH_3	$C_9H_{11}NO_3$	93–94	78	EtOH
2	$N(CH_3)_2$	CH_3	$C_{11}H_{15}NO_3$	206–208 (35)	66	
3	$N(C_2H_5)_2$	CH_3	$C_{13}H_{19}NO_3$	175–178 (10)	71	
4	$NHCH(CH_3)_2$	CH_3	$C_{12}H_{17}NO_3$	183–185 (13)	70	
5		CH_3	$C_{14}H_{19}NO_3$	178–180 (10)	64	
6		CH_3	$C_{13}H_{17}NO_4$	87–88	71	EtOH
7	$NHCH_2C_6H_5$	CH_3	$C_{16}H_{17}NO_3$	71–72	76	EtOH
8	NH_2	C_2H_5	$C_{10}H_{13}NO_3$	121–122	85	EtOH
9	$N(CH_3)_2$	C_2H_5	$C_{12}H_{17}NO_3$	174–176 (11)	72	
10	$N(C_2H_5)_2$	C_2H_5	$C_{14}H_{21}NO_3$	184–186 (13)	83	
11	$NHCH(CH_3)_2$	C_2H_5	$C_{13}H_{19}NO_3$	178–180 (14)	68	
12		C_2H_5	$C_{15}H_{21}NO_3$	204–206 (11)	89	
13		C_2H_5	$C_{14}H_{19}NO_4$	89–90	90	EtOH
14	$NHCH_2C_6H_5$	C_2H_5	$C_{17}H_{19}NO_3$	79–80	77	EtOH
15	NH_2	$CH(CH_3)_2$	$C_{11}H_{15}NO_3$	157–158	87	EtOH
16	$N(CH_3)_2$	$CH(CH_3)_2$	$C_{13}H_{19}NO_3$	168–170 (16)	60	
17	$N(C_2H_5)_2$	$CH(CH_3)_2$	$C_{15}H_{23}NO_3$	172–174 (10)	64	
18	$NHCH(CH_3)_2$	$CH(CH_3)_2$	$C_{14}H_{21}NO_3$	175–177 (10)	61	
19		$CH(CH_3)_2$	$C_{16}H_{23}NO_3$	213–215 (14)	84	
20		$CH(CH_3)_2$	$C_{15}H_{21}NO_4$	203–205 (12)[b]	82	
21	$NHCH_2C_6H_5$	$CH(CH_3)_2$	$C_{18}H_{21}NO_3$	58–59	60	E–PE
22	$N(C_2H_5)_2$	H	$C_{12}H_{17}NO_3$	85–86	64	E–PE
23	$NHCH(CH_3)_2$	H	$C_{11}H_{15}NO_3$	127–128	68	E–EtOH
24		H	$C_{13}H_{17}NO_3$	120–121	70	E–EtOH
25		H	$C_{12}H_{15}NO_4$	108–109	69	E–EtOH

[a] All compds were analyzed for C, H, N. [b] Also mp 56–57°. [c] Purified compds. [d] E, ether; PE, petroleum ether (35–45°).

continued 50 min after completion of the addition at room temp. $Et_3N \cdot HCl$ was removed by filtration and the filtrate was evapd to dryness. To the dry residue was added 5 g of Na_2CO_3 in 50 ml of H_2O (if necessary a few ml of EtOH was added) and the mixture was refluxed for 2 hr. After cooling, the soln was made strongly alkaline with 10% KOH, the mixture was washed with $CHCl_3$, acidified, and extd with $CHCl_3$ and the solvent was evaporated to dryness. Yields and physical constants are given in Table I.

Carcinogenic Activity of Dibenzothiophene Analogs of *p*-Dimethylaminoazobenzene

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Our previous work[1] has shown that replacement of the unsubstituted ring of *p*-dimethylaminoazobenzene (DAB) with heterocyclic rings lead to a number of very active carcinogens and shows some interesting variations among isomers. Now we wish to report the preparation and testing for rat hepatocarcinogenic action of the four isomeric *p*-dimethylaminophenylazodibenzothiophenes (Table I).

TABLE I

N,N-DIMETHYL-*p*-X-DIBENZOTHIENYLANILINE

X[a]	Yield, %	Mp, °C
1	38.6	170–176
2	37.2	184–187
3	20.6	219–220
4	43.5	163–164

[a] All compounds ($C_{20}H_{17}N_3S$) were analyzed for C, H, and N and the results were within ±0.4% of the theoretical value.

Experimental Section[2]

All of the azo compounds were prepared by coupling $PhNMe_2$ with the appropriate aminodibenzothiophenes. A typical procedure is given below. 1- and 2-aminodibenzothiophene were prepared by the procedures developed by Gilman and coworkers[3–5]

* To whom correspondence should be addressed.

(1) E. V. Brown and W. M. Fisher, *J. Med. Chem.*, **12**, 1113 (1969).

(2) All melting points were determined on a Fisher-Johns apparatus and are corrected. The C, H analyses were performed in this department on an F and M Model 185 analyzer by Mr. Daryl Sharp.

(3) H. Gilman and J. F. Nobis, *J. Amer. Chem. Soc.*, **71**, 274 (1949).

(4) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(5) H. Gilman and G. R. Welder, *J. Amer. Chem. Soc.*, **78**, 2906 (1954).