washed,[9] and taken to dryness to give a gum, ν_{max} 3350, 1760 cm^{-1} (neat).

This amino ester in Et_2O (100 ml) was added to 2.0 g of $LiAlH_4$ in Et_2O (20 ml). Following 90 min of heating at reflux the reaction mixture was cooled in ice and treated with 2 ml of H_2O, 2 ml of 15% aqueous NaOH, and H_2O (6 ml). The precipitated solid was collected on a filter and washed (Et_2O). The filtrates were taken to dryness and redissolved in Et_2O. The product was precipitated as its hydrochloride by passing in gaseous HCl.

TABLE IV

AMINO ALCOHOLS

$R^3CH_2CH(NH_2)CH_2OH \cdot HCl$

R^3	% yield	Mp, °C	Formula	Analyses
m-$CF_3C_6H_4$	33	*a*	$C_{10}H_{13}ClF_3NO$	
m-$CF_3C_6H_4Cl$	75	183–186	$C_{11}H_{13}ClF_3NO$	C, H, Cl
m-$CF_3C_6H_4CH_2Cl$	66	188–191	$C_{12}H_{17}F_3NO$	C, H, Cl
$C_6H_4CH_2$	22	108–110	$C_{10}H_{16}ClNO$	C, H, Cl

[a] Could not be recrystallized satisfactorily: sintered at 158°.

Oxazolidinethiones and Thiazolidinethiones.—In a typical experiment a mixture of 0.03 mole of the oily amino alcohol, 2.7 ml of CS_2, 2.48 g of KOH, and 6.4 ml of H_2O in 110 ml of EtOH was heated under reflux for 5.5 hr. The solvent was removed *in vacuo*. The residue was suspended in H_2O and made acidic; the precipitated gum was extracted (Et_2O). The organic layer was washed[9] and taken to dryness. The residual gum (8.09 g) was chromatographed over 800 ml of Florisil. Elution with 10% acetone–Skellysolve B gave first 1.99 g of thiazolidinethione followed by 4.18 g of the oxazolidinethione.

Acknowledgment.—The authors wish to express their appreciation to Dr. G. W. Duncan and Mr. S. C. Lyster for making the results of their biological work available for publication.

Synthesis and Pharmacology of *p*-Methoxycinnamic Acid Derivatives

EUN BANG LEE, KUK HYUN SHIN, AND WON SICK WOO

Natural Products Research Institute, Seoul National University, Seoul, Korea

Received July 9, 1968

In previous publications from our laboratory, it has been reported that *p*-methoxycinnamate shows good antipyretic and analgetic activities.[1] It is rapidly absorbed when administered orally to rabbits and oxidized rapidly *in vivo* to *p*-methoxybenzoic acid which is excreted in the urine as conjugates of glycine and glucuronic acid.[2]

These observations have led us to search for improved potential antipyretic and analgetic compounds. This communication describes the synthesis of several new *p*-methoxycinnamic acid derivatives of salicylic acid and aminophenols, and their preliminary pharmacological properties.

p-Methoxycinnamoylsalicylic acid (I), *p*-acetamidophenyl *p*-methoxycinnamate (II), N-(*p*-methoxycinnamoyl)-*p*-aminophenol (III), and N-(*p*-methoxycinnamoyl)-*p*-phenetidine (IV) were easily obtained by reaction of *p*-methoxycinnamoyl chloride with salicylic acid, *p*-acetaminophenol, *p*-aminophenol, and *p*-phenetidine, respectively.

Pharmacology.—In preliminary pharmacological evaluations all compounds were administered, by the route specified in Table I, as a suspension in 2% aqueous starch solution except that sodium *p*-methoxycinnamate was administered as an aqueous solution. The highest dose employed of a compound having low toxicity was 500 mg/kg. LD_{50} values were calculated by the method of Litchfield and Wilcoxon.[3]

Antipyretic and hypothermal activities were measured by the method described by Almirante, *et al.*[4] In the evaluation of antipyretic activity, drugs were given 5 hr after injection of 0.5 ml of 15% yeast in 10% aqueous acacia mucilage/100 g of body weight into both thighs of the rat. Antipyretic and hypothermal activities were expressed as the temperature indices which constituted the total of the differences between each of the six readings obtained at 60-min intervals for 6 hr after administration of drug and the mean value of two temperature readings 60 min and immediately before administration of drug.

The analgetic activity was assessed by a modification of the hot plate method based on that described by Woolfe and MacDonald.[5] The increases in reaction time were averaged for four observations made at 30-min intervals for 2 hr after administration of drug. The degree of analgetic activity was calculated as the mean per cent increase in thermal pain threshold of treated mice over the average variation of pain threshold of controls. The antiinflammatory effect was investigated by means of the rat-foot edema test,[6] employing 10% yeast suspension in saline, 3.5% formaldehyde–saline, 1% croton oil–olive oil, 10% egg white saline, and 3% dextran–saline as phlogistics. Drugs were given orally immediately before injections of 0.1 ml of each of the phlogistics into the plantar surface of the right hind foot. At 60-min intervals for 5 hr after injection, the volume of the foot was measured by Harris and Spencer's method.[7] The difference between the volume of the foot determined immediately after the injection of phlogistics and the mean value of the five determinations was recorded as that of edema. The activity was expressed as the mean per cent inhibition of swelling in treated rats, compared with that of controls.

The pharmacological results are shown in Table I, which also includes results obtained with the standard drugs such as sodium *p*-methoxycinnamate, acetylsalicylic acid, and acetophenetidine for comparison. All of the compounds lowered body temperature in the yeast-fevered rats. Compound III was the most active antipyretic; however, it affected body temperature in normal rats. Compound I exhibited increased activity compared with that of sodium *p*-methoxycinnamate or acetylsalicylic acid, and, interestingly, had a somewhat more prolonged duration of activity (not shown). All of the compounds synthesized, with the exception of

(1) (a) W. S. Woo, *J. Pharm. Soc. Korea*, **7**, 55 (1963); (b) *ibid.*, **9**, 31 (1965).

(2) (a) W. S. Woo, *ibid.*, **8**, 76 (1964); (b) *J. Pharm. Sci.*, **57**, 27 (1968).

(3) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(4) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, and M. Murmann, *J. Med. Chem.*, **8**, 305 (1965).

(5) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exptl. Therap.*, **80**, 300 (1944).

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(7) J. M. Harris and P. S. Spencer, *J. Pharm. Pharmacol.*, **14**, 163 (1962).

TABLE I

PHARMACOLOGICAL ACTIVITIES OF *p*-METHOXYCINNAMIC ACID DERIVATIVES

Compd	Antipyretic act.[a]	Hypothermal act.[b]	Analgetic act.[c]	Antiinflam act.[d] Yeast	Formaldehyde	Croton oil	Egg white	Dextran	Approx LD_{50},[e] mg/kg
I	13.4	−1.1	57	12	28	34	20	11	630
II	7.7	−0.5	59	2	7	16	11	−2	>3000
III	22.2	12.0	−72	32	5	34	14	22	2570
IV	10.6	−0.2	24	4	9	34	10	−2	>3000
Sodium *p*-methoxycinnamate	6.8	0.2	42	27	9	15	22	12	878[f]
Acetylsalicylic acid	10.5	−0.2	2	34	16	24	24	36	420[g]
Acetophenetidine	14.4	9.0	74	2	5	28	27	18	1008

[a] Total amount of reduction of fever in degrees Centigrade caused by $0.25LD_{50}$ administered intraperitoneally to groups of four fevered rats, in a 6-hr period after treatment (six determinations). [b] Total amount of reduction of body temperature in degrees Centigrade caused by $0.25LD_{50}$ administered orally to groups of four normal rats in a 6-hr period after treatment (six determinations). [c] Per cent increase of pain threshold at $0.33LD_{50}$ administered intraperitoneally to groups of 20 mice. [d] Per cent edema inhibition at $0.25LD_{50}$ administered orally to groups of six rats. [e] Approximate LD_{50}/72 hr was determined by intraperitoneal administration to groups of five mice. [f] Data from ref 1. [g] Data from ref 4.

III, also showed considerable analgetic activity; the average duration of activity of each compound was found not to exceed 60 min (not shown). It is worth noting that mice given III were more sensitive to heat stimuli than untreated mice. However, III showed remarkable reduction of edema formation. Compound I displayed antiinflammatory action equivalent to that of sodium *p*-methoxycinnamate or acetylsalicylic acid.

Experimental Section

Melting points were taken in an open capillary tube in a bath and are uncorrected. Analyses were performed by C. K. Lim of Sung Kyun Kwan University. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The yield shown is from a single experiment, and no attempts have been made to obtain optimal values.

A mixture of 8.9 g (0.05 mole) of *p*-methoxycinnamic acid and 11.9 g (0.1 mole) of $SOCl_2$ was heated at 40° until a clear solution was obtained. The reaction mixture was freed from excess $SOCl_2$ by evaporation under reduced pressure followed by dehydration over NaOH. The crude *p*-methoxycinnamoyl chloride was used for the following procedures without further purification.

***p*-Methoxycinnamoylsalicylic Acid (I).**—A solution of 0.05 mole of *p*-methoxycinnamoyl chloride in 50 ml of dry acetone was added dropwise, with chilling at 0–5° and vigorous stirring, to a solution of 6.9 g (0.05 mole) of salicylic acid in 50 ml of dry pyridine. Stirring was continued for an additional 1 hr, the mixture was refrigerated overnight, and poured into dilute HCl. The precipitate form was filtered, washed (H_2O), and dissolved in saturated $NaHCO_3$. After extraction with Et_2O, addition of dilute HCl to aqueous phase gave a white precipitate. By washing with H_2O and recrystallization from EtOH, colorless prisms were obtained; mp 153–154°, yield 6.7 g (45% based on salicylic acid). *Anal.* ($C_{17}H_{14}O_5$) C, H.

***p*-Acetamidophenyl *p*-Methoxycinnamate (II).**—According to the method used for I, II was prepared from *p*-acetaminophenol (7.5 g, 0.05 mole). The reaction mixture was poured into H_2O. The precipitate formed was recrystallized (EtOH) to give 11.3 g (73%) of II as colorless needles, mp 214–215°. *Anal.* ($C_{18}H_{17}NO_4$) C, H, N.

N-(*p*-Methoxycinnamoyl)-*p*-aminophenol (III).—The same method yielded III from *p*-aminophenol (5.5 g, 0.05 mole). The reaction mixture was poured into H_2O and boiled. The dark brown solid mass formed was decolorized with charcoal and recrystallized from EtOH–H_2O to yield 7.5 g (55%) of III as colorless needles, mp 192–192.5°. *Anal.* ($C_{16}H_{15}NO_3$) C, H, N.

N-(*p*-Methoxycinnamoyl)-*p*-phenetidine (IV).—Dry powdered *p*-phenetidine hydrochloride (8.7 g, 0.05 mole) was added to 100 ml of a benzene solution of *p*-methoxycinnamoyl chloride (0.05 mole) and boiled on a steam bath until HCl gas formation ceased. After cooling, the insoluble mass was filtered off and washed (H_2O). Recrystallization (EtOH) gave 6.0 g (40%) of IV as colorless needles, mp 181–182°. *Anal.* ($C_{18}H_{19}NO_3$) C, H, N.

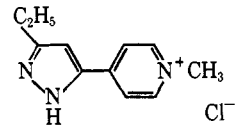
4-(4-Pyrimidinyl)pyridinium Salts. Analogs of the Hypoglycemic 4-Pyrazolylpyridinium Salts

VICTOR J. BAUER, HARRY P. DALALIAN, AND S. R. SAFIR

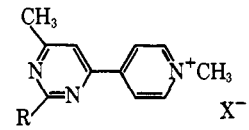
Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received July 23, 1968

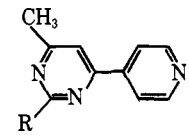
A series of 4-[3(5)-pyrazolyl]pyridinium salts such as **1** has been found to display interesting hypoglycemic activity in normal chicks and alloxan-diabetic mice.[1] In this communication we report the synthesis and results of hypoglycemic testing of several 4-(4-pyrimidinyl)pyridinium salt analogs (**2**).



1



2a, R = H; X = Cl
b, R = OH; X = Cl
c, R = NH_2; X = I



3a, R = H
b, R = OH
c, R = NH_2
d, R = SH
e, R = SCH_3, HCl

Reaction of 4-acetoacetylpyridine[2] with formamide, urea, guanidine carbonate, or thiourea provided the 4-(4-pyridyl)pyrimidines **3a–d**. When **3a–c** were heated with MeCl or MeI, the quaternary salts **2a–c** were formed. Treatment of **3d** with MeCl gave, instead of the desired quaternary salt, the hydrochloride of the S-methyl derivative **3e**. Structures were inferred from

(1) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. Boshart, *J. Med. Chem.*, **11**, 981 (1968).
(2) L. Fabbrini, *Farmaco, Ed. Sci.*, **9**, 603 (1954).