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.

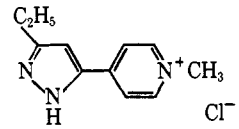
4-(4-Pyrimidinyl)pyridinium Salts. Analogs of the Hypoglycemic 4-Pyrazolylpyridinium Salts

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**).



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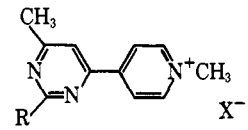
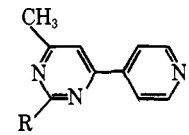


2a, R = H; X = Cl
b, R = OH; X = Cl
c, R = NH_2; X = I



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).

elemental compositions and were confirmed by nmr spectra.[3]

In the nmr spectra of the 4-(4-pyridyl)pyrimidine bases **3a–d**, the pyridyl protons appear as two doublets at τ 1.98–2.05 and 1.22–1.40. Upon quaternization of **3a–c**, these signals shift to new values of τ 1.23–1.43 and 0.84–1.04. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, were found to be diagnostic of pyridine quaternization in our earlier study of pyrazolylpyridinium salts.[1] The newly introduced quaternary methyl groups of **2a–c** appear at τ 5.29–5.50. The salt **3e** fails to display this methyl signal, and instead exhibits a singlet at τ 7.48, consistent with the SCH_3 formulation.[4]

The compounds **2a–c** were tested[5] for hypoglycemic activity in normal mice or chicks. Test compounds were administered orally as saline solutions or carboxymethylcellulose suspensions; controls received an equal volume of vehicle. Blood glucose levels, determined by the method of Hoffman[6] as adapted for the Technicon Auto-Analyzer 2–5 hr after dosing, were not significantly different from controls.

Experimental Section[7]

4-Methyl-6-(4-pyridyl)pyrimidine (3a).—A solution of 23 g (0.14 mole) of acetoacetylpyridine[2] and 100 ml of formamide was heated under reflux for 3 hr, diluted with 500 ml of H_2O, and extrated ($CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to a brown oil, which was chromatographed on 300 g of silica gel. Eluted with $CHCl_3$–MeOH (99:1) was a pale yellow solid. Recrystallization (cyclohexane) gave 1.7 g (7%) of crystals, mp 82–83°, which was sublimed at 150° (0.01 mm) to provide pale yellow crystals, mp 82–83°. *Anal.* ($C_{10}H_9N_3$), C, H, N.

2-Hydroxy-4-methyl-6-(4-pyridyl)pyrimidine (3b).—A mixture of 4.9 g (0.03 mole) of 4-acetoacetylpyridine,[2] 3.0 g (0.05 mole) of urea, 10 ml of HCl, and 50 ml of EtOH was heated under reflux for 16 hr. The solution was concentrated to a small volume under reduced pressure, and the residue was neutralized with NH_4OH. The solid which separated was recrystallized (MeOH) to provide 1.5 g (27%) of colorless crystals, mp 284–286° dec. *Anal.* ($C_{10}H_9N_3O$) C, N; H: calcd, 4.81; found, 5.58.

2-Amino-4-methyl-6-(4-pyridyl)pyrimidine (3c) was prepared by the method of Budesinsky and Musil;[8] tan solid, mp 182–184° (lit.[8] mp 181–182°).

2-Mercapto-4-methyl-6-(4-pyridyl)pyrimidine (3d) was prepared by the method of Longo and Mugnaioni;[9] tan crystals (from DMF), mp 293–295° dec. *Anal.* ($C_{10}H_9N_3S$) C, H, N.

1-Methyl-4-(4-methyl-6-pyrimidinyl)pyridinium Chloride (2a).—A mixture of 1.7 g (0.01 mole) of **3a** and 5 ml of MeCl was heated at 130° in a bomb for 18 hr. The excess MeCl was allowed to evaporate, and the black residue was dissolved in MeOH and treated with charcoal. Addition of ether to the solution gave 2.0 g (90%) of tan solid, mp 252° dec. Recrystallization (*i*-PrOH) provided colorless needles, mp 265° dec. *Anal.* ($C_{11}H_{12}ClN_3$) HCl, N; C: calcd, 59.6; found, 59.0.

1-Methyl-4-(2-hydroxy-4-methyl-6-pyrimidinyl)pyridinium chloride (2b) was prepared in 28% yield from **3b** and MeCl by the method described for the synthesis of **2a**. Recrystallization (MeOH) provided tan crystals, mp 247–248° dec. *Anal.* ($C_{11}H_{12}ClN_3O \cdot 0.5H_2O$) C, H, Cl, N.

1-Methyl-4-(2-amino-4-methyl-6-pyrimidinyl)pyridinium Iodide (2c).—A solution of 1.86 g (0.01 mole) of **3c**, 7.1 g (0.05 mole) of MeI, and 25 ml of MeOH was heated under reflux for 3 hr and cooled. An orange solid, 3 g (91%), mp 279–280° dec, separated and was recrystallized (EtOH) to provide orange crystals, mp 276–277° dec. *Anal.* ($C_{11}H_{13}IN_4$) C, H, I, N.

4-Methyl-2-methylthio-6-(4-pyridyl)pyrimidine hydrochloride (3e) was prepared in 88% yield from **3d** and MeCl by the method described for the synthesis of **2a**. Recrystallization (EtOH) provided colorless crystals, mp 261–262° dec. *Anal.* ($C_{11}H_{12}ClN_3S \cdot 0.5H_2O$) C, H, Cl, N, S.

(3) Extensive studies [A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 339 (1963)] have shown that 2-hydroxy-, 2-amino-, and 2-mercaptopyrimidines exist preferentially as the keto, amino, and thione tautomers. The spectral data on compounds **2b,c** and **3b–d** do not permit unequivocal assignment of tautomeric structures.

(4) Thioanisole exhibits τ 7.53 (S, SCH_3) (N. S. Bhacca, *et al.*, "Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 490).

(5) Testing data were supplied by Drs. D. A. Blickens, S. J. Riggi, and E. C. Tocus of the Metabolic Chemotherapy Department of these laboratories.

(6) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(7) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian A-60 spectrometer with TMS or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard by Mr. W. Fulmor and staff and were as expected.

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1-Imidazolyl Derivatives of 2-Hydroxy-3-phenoxypropane

V. ŠUNJIĆ,[1] D. KOLBAH, F. KAJFEŽ, AND N. BLAŽEVIĆ

KRKA Pharmaceutical and Chemical Works, Institute for Antibiotics, Pharmacy and Technology, Novo mesto, Slovenia, Yugoslavia

Received March 20, 1968

The high antitrichomonal activity of derivatives of 1-substituted 2-methyl-5-nitroimidazole[2,3] on the one hand, and the local anesthetic[4] and β-adrenergic receptor blocking action[5,6] of derivatives of 1-amino-2-hydroxy-3-phenoxypropane on the other hand, suggested the preparation of the title compounds. The low toxicity of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[2] and the high antitrichomonal activity of the compounds containing an ether linkage[7] in position 1 of the imidazole moiety suggested[7] that the compounds of group I might have both of the desired properties. In view of the observed[8] and clinically confirmed[9] effectiveness of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole in the treatment of alcoholism, compounds of group I are of further interest.

In addition to the screening data for analgetic and *in vitro* antitrichomonal activity listed in Table I, preliminary evaluation of the compounds of types II and III has revealed that they have some spasmolytic and muscle relaxant activity; some synergistic effects in these compounds were noted.

(1) Correspondence should be addressed to this author.

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