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NOTES

5-Chloro-2-pyrimidinyl Analog of Dantrolene

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Abstract □ 1-{[5-(5-Chloro-2-pyrimidinyl)furfurylidene]amino}-hydantoin, a structural analog of the skeletal muscle contraction antagonist dantrolene, was synthesized and found to have no skeletal muscle relaxant activity.

Keyphrases □ Dantrolene—synthesis and screening for muscle relaxant activity of 5-chloro-2-pyrimidinyl analog □ 1-{[5-(5-Chloro-2-pyrimidinyl)furfurylidene]amino}hydantoin—structural analog of dantrolene, synthesized and screened for muscle relaxant activity □ Muscle relaxant activity—5-chloro-2-pyrimidinyl analog of dantrolene

The unique skeletal muscle relaxant activity of dantrolene, 1-{[5-(*p*-nitrophenyl)furfurylidene]amino}hydantoin (I), has been demonstrated (1, 2). It has been pharmacologically categorized as a skeletal muscle contraction antagonist (3).

The 5-chloro-2-pyrimidinyl group was shown to replace effectively the *p*-nitrophenyl moiety in a series of nonsteroidal hypocholesterimic agents (II) (4). Thus, the 5-chloro-2-pyrimidinyl analog of the prototype was desired for evaluation for skeletal muscle relaxant activity.

DISCUSSION

Although the requisite 5-(substituted phenyl)-2-furaldehydes were prepared previously by coupling of the appropriate diazonium salt with furfural (5), reaction of diazotized 5-chloro-2-aminopyrimidine with furfural failed to give the desired aldehyde (III). Accordingly, an alternate route to III was devised.

Condensation of furamidine hydrochloride with mucochloric acid, using the general procedure of Budesinsky (6), gave 5-chloro-2-(2-furyl)-4-pyrimidinecarboxylic acid (IV), which was smoothly decarboxylated to 5-chloro-2-(2-furyl)pyrimidine (V) (Scheme I).

Formylation of V gave the aldehyde III, the structure of which is supported by NMR data. Although the NMR spectrum does not completely rule out a 2,3-orientation of substituents in the aldehyde, previous studies in these laboratories showed that 2-phenylfuran is formylated at the 5-position of the furan ring (7). Thus, a 2,5-disubstituted structure was assigned to III.

Treatment of III with 1-aminohydantoin hydrochloride gave VI, the 5-chloro-2-pyrimidinyl analog of I.

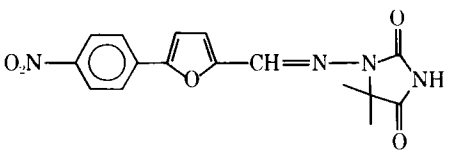
In gross observational testing in mice similar to that described by Irwin (8), VI caused no measurable skeletal muscle relaxation in oral doses up to 1600 mg/kg po. Furthermore, there was no indication of CNS activity or acute toxicity.

Direct skeletal muscle contraction antagonism was tested in the curarized pithed rat gastrocnemius muscle preparation (9). Compound VI did not affect the twitch response of the gastrocnemius muscle over a dose range of 1.0–25 mg/kg iv, indicating that it had no skeletal muscle contraction antagonism activity.

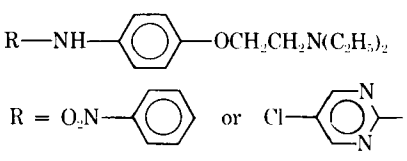
EXPERIMENTAL[1]

5-Chloro-2-(2-furyl)-4-pyrimidinecarboxylic Acid (IV)—Two solutions were prepared: Solution A contained 852 g (15.78 moles) of sodium methoxide in 6360 ml of methanol, and Solution B contained 903 g (5.34 moles) of mucochloric acid in 2285 ml of methanol.

To a solution of 1150 g (7.83 moles) of furamidine hydrochloride in 2610 ml of methanol stirred at 55° was added rapidly 3800 ml of Solution A. The reaction was endothermic. The mixture was reheated to 55°, and 1625 ml of Solution B was added while the mix-

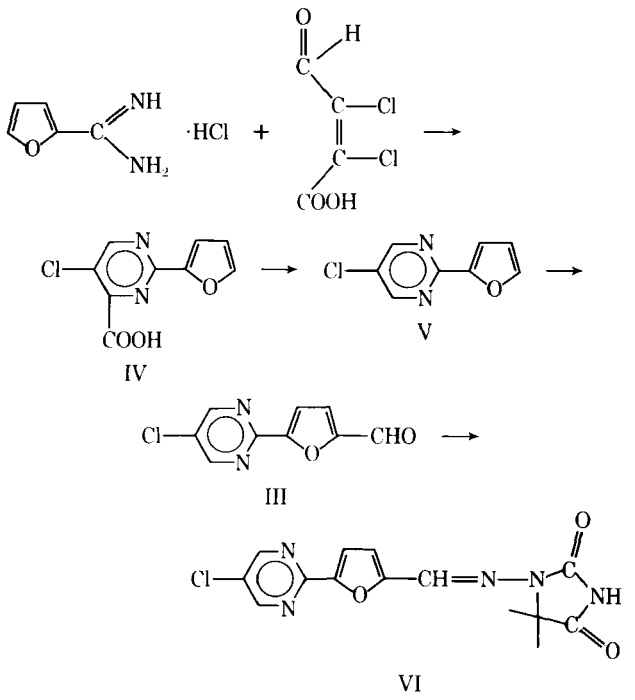


I



II

[1] Melting points were determined on a Mel-Temp apparatus and those below 230° are corrected. IR spectra were determined as mineral oil mulls using a Perkin-Elmer 137B spectrophotometer. The NMR spectrum was obtained on a Varian A-60A instrument and was compared with tetramethylsilane as an internal standard.



Scheme I

ture was maintained at 55–60° with an ice bath. After the mixture was stirred at 55–60° for 15 min, the remainder of Solution A was added. The mixture was reheated to 55°, and the remainder of Solution B was added as already described. The mixture was stirred at 55–60° for 2.5 hr and cooled overnight, and the solid was filtered.

The filter cake was washed with cold methanol, air dried, and taken up in 10 liters of cold water. Acidification with dilute hydrochloric acid gave 473 g (39%) of the product, mp 153–154°. The analytical sample, mp 160–161°, was obtained by recrystallization from water; IR (μm): 5.84 (C=O, acid), 6.32, and 6.41 (C=C, C=N).

Anal.—Calc. for $C_9H_5ClN_2O_3$: C, 48.13; H, 2.24; Cl, 15.79; N, 12.47. Found: C, 48.17; H, 2.34; Cl, 15.86; N, 12.07.

5-Chloro-2-(2-furyl)pyrimidine (V)—The carboxylic acid IV (300 g, 1.33 moles) was heated at 160–170° for 5 min. The cooled mixture was refluxed with 1 liter of chloroform for 1 hr and the suspension was decolorized and filtered. Upon removal of the solvent *in vacuo*, there was obtained 238 g (99%) of the product, mp 106–109°. The analytical sample, mp 108–110°, was obtained by recrystallization from heptane; IR (μm): 6.30 (C=C, C=N) and no C=O absorption at 5.80–6.10.

Anal.—Calc. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; Cl, 19.63; N, 15.51. Found: C, 53.05; H, 3.08; Cl, 19.63; N, 15.00.

5-(5-Chloro-2-pyrimidinyl)-2-furfural (III)—To 1000 ml of dimethylformamide, stirred and cooled at 0–10°, was added 183 ml (307 g, 2.0 moles) of phosphorus oxychloride. To the cooled solution was added a solution of 181 g (1.0 mole) of V in 600 ml of dimethylformamide. The mixture was stirred at 90–100° for 8 hr, cooled, and poured cautiously into 5 liters of 2% sodium hydroxide. An additional 450 ml of 20% sodium hydroxide was added, and the mixture was stirred at room temperature for 30 min.

The mixture was acidified with concentrated hydrochloric acid and the solid was filtered, washed with water, and dried to give 143 g (68%) of the crude aldehyde, mp 179–182°. The analytical sample, mp 209–210°, was obtained by recrystallization from benzene; IR (μm): 6.00 (C=O, aldehyde); NMR (dimethyl sulfoxide-d_6): δ 7.55, 7.70 (doublets, J = 4 Hz, 2, furan C—H), 9.80 (s, 1, aldehyde C—H), and 9.06 (s, 2, pyrimidine C_4-H and C_6-H).

Anal.—Calc. for $C_9H_5ClN_2O_2$: C, 51.82; H, 2.42; N, 13.43. Found: C, 51.79; H, 2.40; N, 13.35.

1-{[5-(5-Chloro-2-pyrimidinyl)furfurylidene]amino}hydantoin (VI)—To a stirred solution of 41.6 g (0.20 mole) of III in 800 ml of dimethylformamide at 50° was added slowly a solution of 60.8 g (0.40 mole) of 1-aminohydantoin hydrochloride in 300 ml of water. The mixture was immediately poured into 3 liters of ice water and the solid was filtered, washed thoroughly with water, and dried. Recrystallization from dimethylformamide–water gave 35 g (57%) of the product, mp 318–320°. The analytical sample, mp 323–325°, was obtained by recrystallization from dimethylformamide–water; IR (μm): 5.63 and 5.79 (C=O, hydantoin).

Anal.—Calc. for $C_{12}H_8ClN_5O_3$: C, 47.15; H, 2.64; N, 22.91. Found: C, 47.20; H, 2.64; N, 22.60.

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