Positional Isomer of the Muscle Relaxant Dantrolene

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Abstract □ 3-[[5-(*p*-Nitrophenyl)furfurylidene]amino]hydantoin, a position isomer of dantrolene, was synthesized and evaluated for skeletal muscle relaxant activity.

Keyphrases □ Dantrolene positional isomer (3-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin)—screened for skeletal muscle relaxant activity □ 3-[[5-(*p*-Nitrophenyl)furfurylidene]amino]hydantoin (dantrolene positional isomer)—screened for skeletal muscle relaxant activity □ Skeletal muscle relaxant activity—3-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin (dantrolene positional isomer) screened

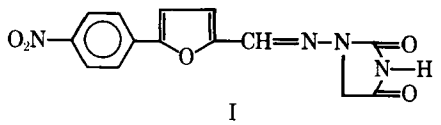
Dantrolene, 1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin (I), was shown previously to demonstrate unique skeletal muscle relaxant activity (1, 2) by a direct action on skeletal muscle. It has been pharmacologically categorized as a skeletal muscle contraction antagonist (3). This report describes the synthesis of 3-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin (II), a positional isomer of I, and the evaluation of this compound for skeletal muscle relaxant activity.

DISCUSSION

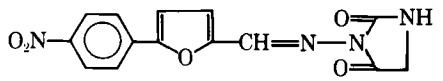
The reaction of 5-(*p*-nitrophenyl)-2-furaldehyde (III) with 3-aminohydantoin (IV) (4) by a previously described method (5) gave the target Compound II.

When using gross observational techniques similar to those described by Irwin (6), II did not produce any evidence of muscle relaxation or any other pharmacological activity at doses from 200 to 1600 mg/kg po. No toxicity was noted over the same dose range.

In the pithed rat gastrocnemius muscle preparation (7), a dose of 25 mg/kg iv administered in tetrahydrofurfuryl alcohol (0.75 ml/kg) caused a 25.3 ± 1.8% decrease in the twitch response. The solvent itself produced no significant effect on the twitch response, while dantrolene administered at the same dose caused a 70% decrease in the twitch response (7). This twitch inhibition indicates that II has slight contraction antagonist activity but that potency and effectiveness are less than that of dantrolene.



I



II

EXPERIMENTAL[1]

Compound II was prepared as follows. The reaction of III and IV by a previously described method (5) gave II, mp 233–234°. The analytical sample, mp 268–269°, was obtained by recrystallization from nitromethane; IR (μm): 5.61 and 5.80 (hydantoin C=O); NMR (dimethyl sulfoxide-d_6): δ 4.03 (s, 2, hydantoin CH_2), 7.28, 7.44 (doublets, J = 3.5 Hz, 2, furan C—H), 7.98, 8.28 (2 doublets, J = 9.0 Hz, 4, phenyl C—H), 8.28 (m, 1, N—H), and 9.23 (s, 1, =C—H).

Anal.—Calc. for $C_{14}H_{10}N_4O_5$: C, 53.50; H, 3.21; N, 17.83. Found: C, 53.51; H, 3.24; N, 18.03.

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[1] Melting points were determined on a Mel-Temp apparatus and are uncorrected. The IR spectrum was determined as a mineral oil mull 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.