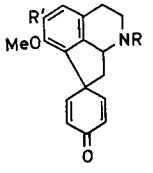
**Some pharmacological activities of crotonosine and pronuciferine**

SIR,—Crotonosine (Ia) and pronuciferine (Ib) are pro-aporphines isolated from *Croton Linearis* Jacq, a common plant in Jamaica (Haynes & Stuart, 1963; Haynes, Stuart, Barton & Kirby, 1966).




a. R = H, R′ = OH
b. R = Me, R′ = MeO

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A preliminary estimation of their local anaesthetic activity by the guinea-pig method of Bulbring & Wajda (1945) indicated them to be potent local anaesthetics compared with procaine and lignocaine (Fig. 1). The LD50 of pronuciferine by intraperitoneal injection in mice is 120 mg/kg while that of crotonosine is 1·20 g/kg (Stuart, 1963).

On the guinea-pig isolated ileum, small doses of either compound (pronuciferine, 0·001–1·0 μg/ml; crotonosine, 0·1–10·0 μg/ml) increase the contractions obtained with acetylcholine while larger doses (pronuciferine, 5–200 μg; crotonosine, 100–200 μg/ml) inhibit the actions of acetylcholine and nicotine on the preparation.

With the rat phrenic nerve diaphragm preparation stimulated electrically at a frequency of 6/min (Bulbring, 1946), small doses of either compound (4 μg/ml) increase the response to electrical stimulation while large doses (400 μg/ml) inhibit the response. Pretreatment of the preparation with neostigmine (40 μg/ml) increases the inhibition by crotonosine (400 μg/ml) but reduces the inhibition by pronuciferine (400 μg/ml).

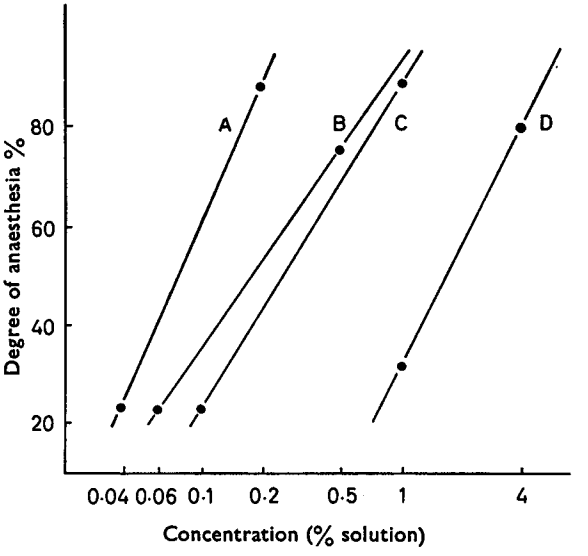


FIG. 1. Mean results of a comparison of local anaesthetic activity of the hydrochlorides of (A) crotonosine, (B) pronuciferine, (C) lignocaine, (D) procaine.

On the toad (*Bufo marinus*) rectus abdominis preparation, both crotonosine and pronuciferine (1–500 $\mu$g/ml) increase the contractions obtained with acetylcholine, and at a concentration of 50 $\mu$g/ml they antagonise the action of (+)-tubocurarine on this preparation.

Crotonosine causes an initial stimulation followed by depression, but pronuciferine causes only depression on the chick biventer cervicis nerve-muscle preparation (Ginsborg & Warriner, 1960) at 200–400 $\mu$g/ml.

The observed inhibitory effects of crotonosine and pronuciferine on these three preparations are consistent with the local anaesthetic activity of the compounds (see de Elio, 1948; Feldberg & Lin, 1949; Kosterlitz & Lees, 1949; Sinha & West, 1953; Green & Hughes, 1966). However, crotonosine and pronuciferine differ from other local anaesthetics in that in small doses they potentiate the chemical and electrical stimulation of these preparations. Whether they first stimulate the release of acetylcholine before inhibiting it is the subject of further investigation.

These two compounds inhibit all the skeletal muscle preparations examined, but seemingly by differing mechanisms. Judging from their difference in behaviour toward neostigmine on the rat phrenic diaphragm preparation and towards the chick biventer cervicis preparation it seems that crotonosine resembles a depolarizing neuromuscular blocking agent while pronuciferine resembles a competitive neuromuscular blocking agent.

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