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SOME AMINOCOUMARIN DERIVATIVES POSSESSING LOCAL ANESTHETIC ACTIVITY

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The general structural requirements for a local anesthetic is a lipophilic moiety containing an aromatic nucleus joined to a hydrophilic moiety containing a tertiary amino group through an intermediate alkyl chain. Since many coumarin derivatives exhibit physiological activity[1–3] it was thought interesting to synthesize coumarin derivatives incorporating the above structural features. The synthesis of substituted aminoacetamidocoumarins was therefore undertaken and the local anesthetic activity tested.

The first step in the synthesis of these compounds is the preparation of 3- and 6-N-chloroacetylamino-coumarins by the reaction of chloroacetyl chloride on 3- and 6-amino-coumarins[4,5]. 4-Aminocoumarins failed to react with chloroacetyl chloride. Treating a solution of the aminocoumarin (0·01 mole) in dioxane (minimum volume) with chloroacetyl chloride (0·02 mole) for 3 hr afforded the chloroacetyl-amino-coumarins as crystalline solid from alcohol in 70–80% yield. The IR spectrum of a typical compound is as follows: 3450, 3400, 3260 (–NH), 1660, 1620 (>C=O), 1600, 1560, 1540 cm^{-1} (aromatic).

The chloroacetylaminocoumarin (0·01 mole) and the amine (0·015 mole) were dissolved in tetrahydrofuran and kept at 30° C for 24 hr. The filtrate was evaporated to give the aminoacetamidocoumarins in about 70% yield, crystallized from benzene-petroleum ether (100–120°). The IR spectrum of 6-N-[morpholino]-acetamidocoumarin is as follows:

3300 (–NH), 1700, 1610 (>C = O), 1540, 1490 cm^{-1} (aromatic) (Table I).

The pharmacological testing of the substituted amino-acetamidocoumarins was carried out as follows:

The rat hemidiaphragm was mounted on a rat phrenic nerve diaphragm holder and suspended in a 40 ml bath of Kreb's solution, bubbled with oxygen and maintained at 37° C. The muscle was stimulated directly using a square wave impulse of pulse width 0·5 m sec (20–30 volts) and a frequency of 0·1 Hz. The contraction was picked up by a Force Displacement Transducer and the signal amplified using a 10 μ volt universal bio-amplifier and recorded on a 4-channel INCO-polygraph. Control tracings were obtained for 5 minutes and the drugs were added in doses of 0·5, 1·0, 2·0 and 4 mg at intervals of 5 min in a cumulative fashion. The percentage inhibition

Table I

Aminocoumarin	M.P. ° C	Amine condensed	Acetamidocoumarin	M.P. ° C
3-N-Chloroacetyl	194–96	Pyrrolidine	3-[N-pyrrolidino]-	118–20
		Piperidine	3-[N-piperidino]-	148–50
		Morpholine	3-[N-morpholino]-	152–54
6-N-Chloroacetyl	206–08	Pyrrolidine	6-[N-pyrrolidino]-	110–12
		Piperidine	6-[N-piperidino]-	152–54
		Morpholine	6-[N-morpholino]-	185–87
6-N-Chloroacetyl-7-methyl-	195–97	Pyrrolidine	7-Methyl-6-[N-pyrrolidino]-	100–02
		Piperidine	7-Methyl-6-[N-piperidino]-	128–29
		Morpholine	7-Methyl-6-[N-morpholino]-	193–94

All the compounds gave satisfactory elemental analysis.

TABLE II

Compound (as hydrochloride)	Bath concentration (mg per ml)	% Inhibition
3-[1-Pyrrolidino]-acetamidocoumarin	0·5	26·3
	1·5	89·5
	2·0	100·0
3-[1-Piperidino]-acetamidocoumarin	1·0	60·5
	3·0	97·0
3-[1-Morpholino]-acetamidocoumarin	0·5	4·5
	1·5	20·4
	3·5	49·5
	7·5	86·0
Procaine	0·5	22·7
	1·5	50·0
	3·5	100·0

for the bath concentrations of the most active compounds is shown in Table II. Procaine hydrochloride was used as standard.

The 6-(N-substituted amino) acetamidocoumarins required a bath concentration between 7 and 15 mg/ml to show complete inhibition of the contractions.

Pharmacological testing was carried out at the Haffkine Institute, Bombay. We are grateful to the UGC for financial assistance to GM.

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PLEISTOCENE *TUBIPORA* FROM TANZANIA (EAST AFRICA)

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SHROCK AND TWENHOFEL[1] and Bayer[2] state that the common Indo-Pacific reef coral *Tubipora* is only of a Recent genus, a fossil *Tubipora* Linne 1758 is reported for the first time in Tanzania. *T. purpurea* is known from Pleistocene reefs in Kenya (Gregory[3]) and from the Plio-Pleistocene of Port Sudan Montanaro[4]. Further *T. rubiola* is reported from the Plio-Pleistocene of Timor (Felix[5]). Umbgrove[6] describes *Tubipora* sp. from Upper Miocene of Java, and Yabe and Sugiyama[7] record fossil and living *Tubipora* from Japan.

In Tanzania the fossil *Tubipora musica* occurs in the Wazo Hill limestone of Pleistocene age. The limestone is exposed in the Wazo Hill quarry (6° 39′ S; 39° 09′ E) 25 km NW of Dar es Salaam.

The corallum is massive, oval or semicircular in shape. The corallites consist of long, slender tubes of calcium carbonate (length 3–7 cm, diameter 0·2–0·3 cm) (Fig. 1). They are almost parallel, closely spaced and radiating outwards. The tubes are partitioned by transverse platforms or stolons containing solenia (Figs. 1 and 2). New corallites arise from stolons and never bud from old corallites. The wall of the tubes is perforate.

Specimens of Recent *T. musica* from the Tanzanian coast (Fig. 2) show great variability in tube diameter, distance between transverse platforms and thickness of tube wall and stolon. The dimensions of the newly discovered Pleistocene species fall well within the variability of the Recent species and therefore it is assigned to the same species of *T. musica*.

Stratigraphically the Wazo Hill quarry shows barren clay-bound sands at the base with Wazo Hill coral limestone (8–20 m) in the middle and topped by the lateritic soil (2–4 m).

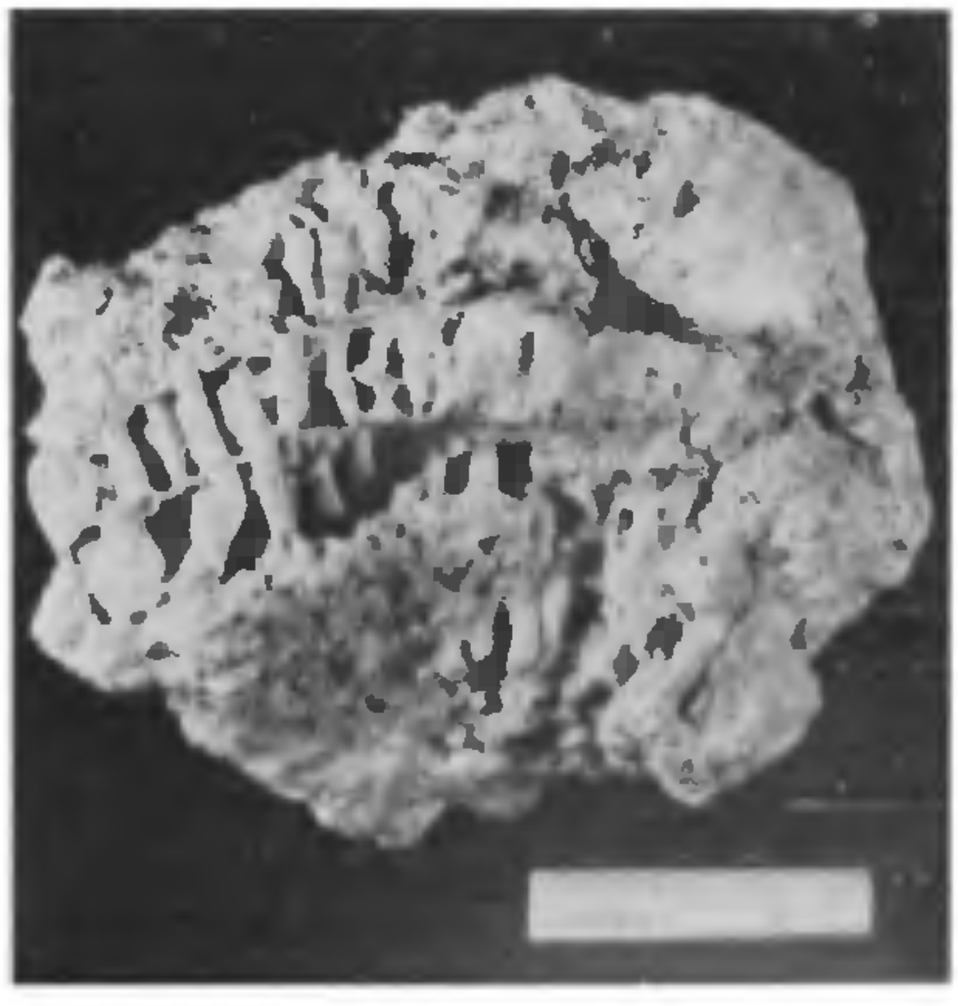

FIG. 1. A colony of Pleistocene *Tubipora musica* Linne 1758 showing the cylindrical tubes and transverse platforms.