Vasopressor responses to kallidin, bradykinin and eledoisin in hypotensive rats

SIR,—There have been a few reports in the literature of pressor responses being obtained after injections of the normally vasodilator polypeptides bradykinin, kallidin and eledoisin. Thus, Croxatto & Belmar (1961) have shown that bradykinin is hypertensive in nephrectomised rats and in normal rats treated with the ganglion blocking drug pentolinium, whilst Erspamer & Glässer (1963) have reported hypertensive responses to eledoisin in decapitated chickens, in pithed rats and in rats pretreated with hexamethonium. The latter authors have produced evidence that the hypertensive actions of eledoisin are mediated through the adrenal medulla. Move direct evidence of the ability of bradykinin and kallidin to release adrenaline from the adrenal medula has also been provided recently by Feldberg & Lewis (1963). These authors injected the two plasma kinins into the coeliac artery of eviscerated cats and detected adrenaline in the venous affluent.

Bradykinin has recently been shown to be pressor in the cat during pregnancy (Parratt, 1964) and this observation has led to an examination of the vascular effects of the polypeptides bradykinin, kallidin and eledoisin in pregnant rats. The following is a summary of these observations.

Bradykinin and kallidin are initially purely hypotensive both in pregnant and in non-pregnant rats when injected intravenously in doses of 0·5–2·0 μg/kg. After repeated injections of these plasma kinins at intervals of 5 min however, this hypotensive response changes to a diphasic one, or is even purely hypertensive, provided the injections are continued for a period of from 1–3 hr. This evidence does not suggest any major difference in the vascular response of the rats to these polypeptides during pregnancy.

In both normal and pregnant rats with a blood pressure of 30–50 mm Hg, all three polypeptides raise the blood pressure when injected intravenously in doses of 0·5–5 μg/kg (for bradykinin and kallidin) or 0·25–1 μg/kg (for eledoisin). This is so whether the blood pressure has been lowered by ganglion blockade (pentolinium tartrate, 1 mg/kg intravenously), by acute haemorrhage, by overdose of the anaesthetic used (pentobarbitone sodium) or by injecting large doses of either polypeptide. These pressor responses are abolished by acute bilateral adrenalectomy, and are abolished or markedly reduced by pretreatment with reserpine (5 or 10 mg/kg, intraperitoneally 24 hr. previously) or by acute pretreatment with the α-adrenergic blocking drug rogitine in doses (1–2 mg/kg) which reverse the normal pressor response of the rat to adrenaline. On some occasions the pressor responses produced by kallidin and bradykinin were reversed by rogitine in a similar way to those of adrenaline. Pressor responses to all three polypeptides, and to adrenaline could be re-obtained after waiting for the effects of α-blockade to wear off.

These experiments suggest that kallidin, bradykinin and eledoisin are able, in hypotensive rats, to release catecholamines from the adrenal medulla. This may also contribute to the vascular effects of these polypeptides when they are injected into normotensive animals.

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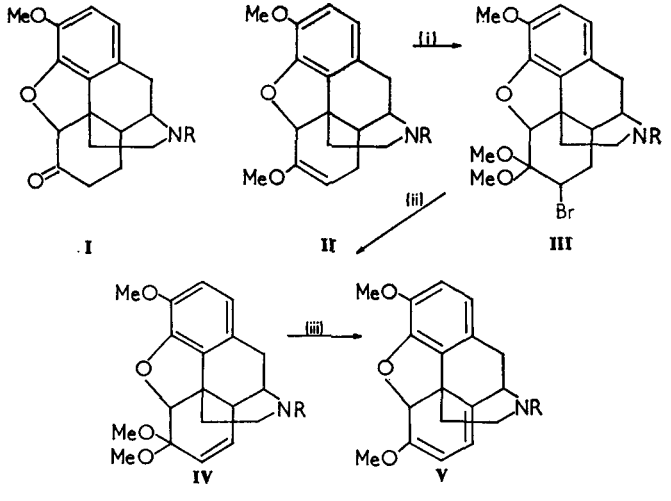
The synthesis of *N*-allylnorthebaine

SIR,—*N*-Allynorthebaine (V; R = $CH_2:CH\cdot CH_2$) is of major importance in the study of the structure-activity relationships of the morphine alkaloids and their derivatives. We now report the synthesis of *N*-allylnorthebaine, *N*-cyclopropylmethylnorthebaine, *N*-(t-butoxycarbonyl)northebaine, and of northebaine (V; R = H) itself.

O-Methylation of *N*-benzyloxycarbonyldihydronorcodeinone (I; R = $PhCH_2O\cdot CO$) with methyl sulphate and sodium t-butoxide gave the enol ether (II; R = $PhCH_2O\cdot CO$), which on treatment with triethylsilane in the presence of palladium chloride and triethylamine, followed by addition of methanol (Birkofer, Bierwith & Ritter, 1961), gave Δ^6-dihydronorthebaine (II; R = H), m.p. 153–154°. This product was converted into northebaine (V; R = H) [salicylate, m.p. 192·5 — 193·5° (decomp.)] by the route illustrated, with is analogous to that employed by Rapoport and his co-workers in the synthesis (Rapoport, Reist & Lovell, 1956) of thebaine itself from Δ^6-dihydrothebaine (II; R = Me) (Homeyer, 1956). Alkylation of northebaine with allyl bromide, or, better, alkylation of the ketal (IV; R = H) followed by treatment with anhydrous toluene-*p*-sulphonic acid in chloroform, gave *N*-allylnorthebaine (V; R = $CH_2:CH\cdot CH_2$)(salicylate, m.p. 185–187°). An alternative synthesis started from the ketone (I; R = $Bu^tO.CO$), itself obtained on treatment of dihydronorcodeinone (I; R = H) with t-butyl azidoformate (Schwyzer, Sieber & Kappeler, 1959; the reagent was prepared according to Carpino, Giza & Carpino, 1959). Further stages, analogous to those already described, led to *N*-(t-butoxycarbonyl)northebaine (V; R = $Bu^tO\cdot CO$), which on further treatment with toluene-*p*-sulphonic acid gave northebaine.



(i) MeOBr (ii) $EtMe_2COK$ (iii) p-$Me\cdot C_6H_4\cdot SO_3H$