THE INOTROPIC ACTIVITY OF 4-PHENYL-7-ALKYL-6,8-DIOXO-4,5,8a,9-TETRAHYDRO-1H-DIIMIDAZO [3,4-a:4,5-d] PYRIDINES AND 2-ALKYLPIPERIDINO [1,2-c] IMIDAZOLIDINE-1,3-DIONES

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Selective positive inotropic activity has previously been observed in the 6,8-dioxo-4,5,8a,9-tetrahydro-1H-diimidazo[3,4-a:4,5-d]pyridines (1, R=H, n-Pr, C_6H_5) and in the 1,3-dioxo-5H-10,10a-dihydroimidazo[3,4-b]isoquinolines (2, R=Et., n-Pr) (Fraser & others, 1977). In guinea-pig isolated atria 2, R=n-Pr at 54μg ml^{-1} and 1 R=C_6H_5 at 100μg ml^{-1} caused respectively a 109% and a 75% increase in force when compared with the standard (-)-isoprenaline, and both produced a slight decrease in rate. The title compounds (Table 1) were synthesised to further delineate molecular features associated with positive inotropism.

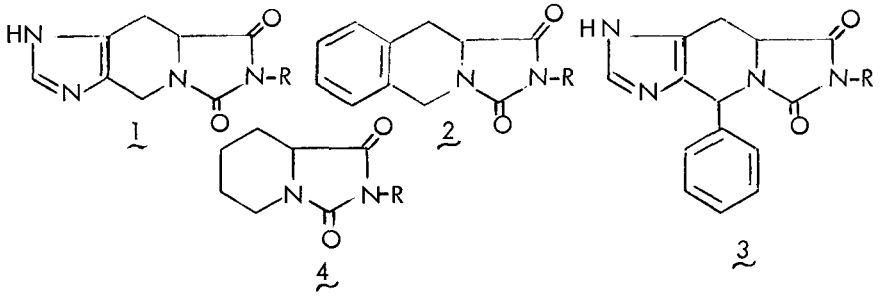

Table 1. Cardiotonic effects of selected 4-phenyltetrahydrodiimidazo[3,4-a:4,5-d]pyridines (3) and piperidino[1,2-c]imidazolidines (4)

Structure	R	Increase Tension		Rate
		EC50(μg ml^{-1})	% of maximum to(-)-isoprenaline	Decrease as% resting rate
3	Me*	24	10	NSE
	Et**	43	6	NSE
	n-Pr*	137	18	NSE
	iso-Pr**	55	7	NSE
	cyclo-C_6H_{11}**	30	4	NSE
	Ph**	100	NSE	NSE
4	Me^+	30	8	NSE
	$n\text{-}Pr^+$	14	12	NSE

Footnotes to Table 1. *Maleate **Hydrochloride +Only water-soluble members of series NSE = no significant effect.

The introduction of a phenyl group at the 4 position of the tetrahydro-1H-diimidazo-[3,4-a:4,5-d]pyridines (1) reduces inotropic activity which could reflect either an unfavourable steric effect or diminished partitioning at the receptor. The piperidino[1,2-c]imidazolidine-1,3-diones (4) which represent the nucleus common to all of the compounds examined retain weak, but perhaps significant, activity.

Fraser, E.C., Smail, G.A., Lumley, P. (1977) J. Pharm. Pharmac. 29: 79P