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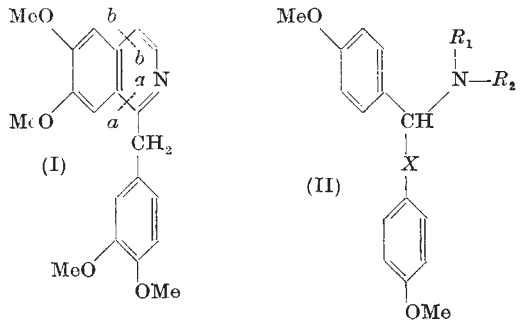
New Synthetic Antispasmodics

A RECENT publication[1] prompts us to report the preparation of a number of novel synthetic antispasmodics related to papaverine. The numerous synthetic analogues of papaverine (I) which have been prepared (see, for example, Blicke[2]) can be divided into two main groups: (1) those with an intact *iso*quinoline ring system (for example, eupaverine[3]) and (2) those in which the *iso*quinoline ring has been opened at the line *a*—*a* to give a *bis*-(2-phenylethyl)amine (for example, sestron[4]).



A third type of papaverine analogue, obtained by opening the *iso*quinoline ring along the line *b*—*b*, does not seem to have been investigated (except that α-diethylamino-4-methoxy deoxybenzoin is reported[5] to have half the antispasmodic activity of papaverine in an isolated observation), and we now report the synthesis and activities of a series of compounds of that type.

A series of N-alkyl-1 : 2-di-(*p*-methoxyphenyl)-ethylamines (II ; $X = CH_2$), N-alkyl-α-aminodeoxyanisoins (II ; $X = CO$), and N-alkyl-2-amino-1 : 2-di(*p*-methoxyphenyl) ethanols (II ; $X = CHOH$) were prepared and, in view of the promising activity of certain 1-phenyl *iso*quinoline compounds, in which the methylene bridge was omitted (for example, neupaverine[3]), a number of N-alkyl-di-(*p*-methoxyphenyl)-methylamines (II ; $X = -$) were also synthesized for this work.

Tested on isolated guinea pig ileum against spasms produced by barium chloride and carbachol, using papaverine and atropine as standards, all compounds exhibited spasmolytic activity. In order to obtain a valid comparison, the relative potencies are quoted on a molar basis (see Table 1).

Table 1. SPASMOLYTIC ACTIVITIES

Compound II			Relative potency (molar)	Compound II			Relative potency (molar)
X	R_1	R_2		*X*	R_1	R_2	
CO	H	Me	0·9	CH_2	H	H	0·8
CO	H	Et	1·2	CH_2	H	Et	0·9
CO	H	*iso*Pr	0·3	CH_2	H	*iso*Pr	1·2
CO	Me	Me	3·3*				
CO	Et	Et	0·2*				
CHOH	H	Me	0·8	—	H	H	0·8
CHOH	H	Et	0·8	—	H	Me	1·8
CHOH	H	*iso*Pr	0·5	—	H	Et	0·8
CHOH	Me	Me	0·2*	—	Me	Me	1·1
CHOH	Et	Et	1·2*	—	Et	Et	1·0
Papaverine			1·0	—	H	*iso*Pr	0·6

* With these compounds spasm of the guinea pig ileum was induced with posterior pituitary extract.

Relative neurotropic activity was between 0·005 and 0·2 of atropine, and acute toxicities (intravenous in mice) were uniformly between 60 and 80 mgm./kgm. for all series ; that is, with an LD_{50} of two to three times that of papaverine (LD_{50} = 30 mgm./kgm.). In view of these promising results, these and other related compounds are undergoing further investigation, and details will be reported in full elsewhere.

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Efficiency of Oxidative Phosphorylation

THE quantitative yield of phosphate fixed during cellular oxidations deserves critical investigation, for it determines the efficiency with which utilizable energy may be derived from assimilated foodstuffs and it may influence metabolic regulatory mechanisms[1]. This problem has been the subject of many investigations (cf. Krebs *et al.*[2] and Slater and Holton[3]). In general, the observed yield has increased over a period of years as newer methods of measurement have been developed and particularly as more knowledge has been made available concerning the preparation of undamaged mitochondria which are free from interfering cellular components.

For example, Ochoa[4], in 1944, observed a phosphorus/oxygen ratio of 1·4–1·7 for the single-step oxidation of α-ketoglutarate to succinate by a dialysed extract of cat heart. By correcting for previously measured losses of high-energy phosphate occurring in the system, a value of 3 for the actual ratio was deduced. In more recent investigations with mitochondria prepared from liver heart muscle by the procedure of Schneider[5], the same oxidative reaction proceeds with measured phosphorus/oxygen ratios greater than 3 [2,6,7].

Slater, Cleland and Holton, in an extensive study of heart sarcosomes[3,8], have consistently obtained