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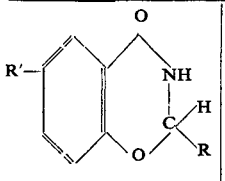
Structural requirements for the antiphlogistic activity in some novel derivatives of chlorthenoxazin

SIR,—Kadatz (1957) described the synthesis and the anti-inflammatory properties of chlorthenoxazin, a benzoxazine derivative [2-(2-chloroethyl)-2,3-dihydro-4-oxobenz-1,3-oxazine]. Some years later Baroli, Bottazzi, Ferrari, Garzia, Trabucchi & Vargiu (1963), Ferrari & Garzia (1963), Arrigoni-Martelli (1964) and Arrigoni-Martelli & Conti (1964) described the synthesis and the pharmacological properties of some new derivatives of this compound with various substituents on the nucleus, particularly the 6-amino-derivative (A 350). For the purpose of investigating more deeply the structure-action relationships of this class of compounds, we synthesised a number of new derivatives of chlorthenoxazin (AP 67). The anti-inflammatory activity has been studied on three experimental models of phlogosis of the hind paw of the rats: carrageenin-, dextran-, formalin-oedema (for methods see Arrigoni-Martelli, 1964; Arrigoni-Martelli

TABLE 1. ANTI-INFLAMMATORY ACTIVITY

	Dose mg/kg oral	% Inhibition (± s.d.) of oedema induced by:			Oral LD 50 mg/kg (with confidence limits), rat
		Carrageenin	Dextran	Formalin	
R = CH_2–CH_2–Cl R′ = H (AP 67) Chlorthenoxazin	200	37·0 (±3·2)	22·9 (±4·8)	12·1 (±3·6)	> 2000
R = CH_2–CH_2–Cl R′ = NH_2 (A 350)	195	54·9 (±1·9)	38·8 (±4·2)	27·5 (±4·2)	1958 (1847–2024)
R = Et R′ = H (A 301)	131	33·0 (±2·8)	24·2 (±4·7)	15·6 (±3·9)	1310 (1156–1573)
R = Et R′ = NH_2 (A 302)	189	41·5 (±2·2)	35·3 (±5·1)	18·1 (±3·4)	1890 (1756–1981)
R = Me R′ = H (A 309)	102	25·8 (±2·4)	22·3 (±4·8)	7·5 (±3·1)	1025 (851–1270)
R = Me R′ = NH_2 (A 310)	141	35·8 (±3·1)	32·6 (±5·9)	12·3 (±3·9)	1415 (1282–1593)
R = $CHMe_2$ R′ = H (A 319)	185	20·5 (±2·9)	12·7 (±6·4)	6·4 (±2·1)	1850 (1781–2021)
R = $CHMe_2$ R′ = NH_2 (A 321)	200	26·4 (±2·5)	20·9 (±5·8)	16·6 (±3·9)	> 2000
Phenylbutazone	128	48·2 (±3·1)	29·9 (±4·7)	28·6 (±5·4)	1280 (1156–1325)

& Conti, 1964). The results obtained with some selected compounds—reported in Table 1—show the following:

(1) The presence of the NH_2-group on the C-6 of the nucleus increases the antiphlogistic activity independently from the length and the shape of the side-chain. The acute toxicity is unchanged or diminished.

(2) The replacement of the methyl group on the side-chain with an ethyl-group led to an increase of the antiphlogistic activity.

(3) The branching of the side-chain led to a reduction of the antiphlogistic activity.

(4) The presence of the chloroethyl-group on the side-chain confers a more pronounced anti-inflammatory activity, particularly when its presence is accompanied by the introduction of NH_2-group on the C-6 of the nucleus.

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Role of the polymethylene chain in derivatives of demecarium bromide on the inhibition of monoamine oxidase

SIR,—Inhibition of monoamine oxidase has been shown by several structurally unrelated compounds. We have recently reported (Pant, Parmar & Bhargava, 1964) that demecarium bromide [decamethylene-bis(3-dimethylaminophenyl *N*-methylcarbamate)dimethobromide], a potent inhibitor of brain acetylcholinesterase inhibits monoamine oxidase present in isolated rat liver mitochondria. In the present study the effect of the tetramethylene, hexamethylene, octamethylene and dodecamethylene derivatives as well as the decamethylene derivative has been investigated on monoamine oxidase in rat liver mitochondria to show the effect of the number of methylene groups connecting the two neostigmine molecules present in these compounds.

Monoamine oxidase activity was determined by the conventional Warburg manometric method (Creasey, 1956). The oxygen uptake has been shown by Parmar & Nickerson (1961) to reflect the true enzyme activity during oxidative deamination of tyramine. The effect of these compounds was also investigated on the oxidation of tryptamine. The inhibition of monoamine oxidase produced by these compounds at the final concentration of 8×10^{-5}M using tyramine and tryptamine as substrates is shown in Table 1. Inhibition of the enzyme increased with increase in the number of methylene groups in the compounds during oxidative deamination of tyramine or tryptamine. The compound with 4 methylene groups had no inhibitory effect on the enzyme activity at this concentration. Further increase in its concentration to $3{\cdot}2 \times 10^{-3}$M also produced no