SPASMOLYTIC ACTIVITY OF 3-SUBSTITUTED-4-QUINAZOLONE DERIVATIVES

By

K. KAR, R.N. SUR AND N.N. DE

Central Drug Research Institute, Lucknow

(*Received January 7, 1963*)

Of the 21 derivatives from 3-substituted-4 quinazolone, four compounds viz. 3-β-dimethylaminoethyl-4-quinazolone phenylethyl bromide, 3-β-diethylaminoethyl-4-quinazolone hydrochloride, 3-β-diethylaminoethyl-4-quinazolone benz bromide and 3-β-di-n-propylaminoethyl-4-quinazolone hydrochloride were found to have marked antispasmodic activity against acetylcholine and histamine.

A series of 3-β-(and γ)-dialkylaminoethyl-(and propyl)-4-quinazolones and quinazolo-4-thiones and their quaternary salts synthesised by Bhaduri, Khanna and Dhar (1962) have been investigated for their antispasmodic activity. This paper communicates the preliminary pharmacological observations on 21 derivatives of such series examined.

METHODS

Acute Toxicity.—A rough idea of the approximate lethal dose (ALD) for the chemical agents in mice was determined by the method of Varma *et al* (1959). One animal was injected intra-peritoneally with a single dose of a test compound in volumes not exceeding 0·3 ml. Each compound was used at several dose levels : 50, 100, 150, 200 or higher multiples of 50 mg/kg. The minimum dose killing the animal was taken as the ALD. Further checking of this dose was made by injecting an amount intermediate between ALD and the preceding maximum tolerated dose in 2 mice which were observed for three days for any mortality.

Isolated Intestine.—Five centimetres long terminal portions of ileum were taken from guineapigs weighing approximately 600 g and suspended in oxygenated Tyrode solution at 35-36°C in isolated organ bath of 60 ml capacity. After half an hour rest, 2-4 doses of spasmogens were added to the bath to obtain uniform amplitude of contraction which was recorded kymographically. The spasmogen used, acetylcholine chloride (5×10^{-7} g) and histamine acid phosphate (2×10^{-6} g) were allowed to act for 10 seconds. The aqueous solutions of the test compounds were added to the bath 1 min

before the addition of the spasmogen. The tissue was washed twice at 1 min interval and 3 min rest was given to it unless otherwise stated Effect of graded doses of test compounds on the spasmogen induced contraction was noted and the amplitude of contraction was measured in millimetre to determine the per cent reduction of contraction corresponding to the doses of the test compounds used. The dose causing 50 per cent reduction of contraction (ED_{50}) was calculated by plotting log dose-percentage inhibition curve.

The compounds which showed marked effect were further tested on the rabbit ileum to study their effect on tone, spontaneous motility and barium-induced contraction in the same way as described for guineapig ileum.

Cardiovascular effects.—The effects of the most active compounds were also studied on the rate and amplitude of isolated guineapig heart perfused with Ringer-Locke solution under constant pressure by Langendorff method. The test substances in 0 5 ml were slowly injected into the perfusion fluid.

The effect of these test compounds was studied on the carotid blood pressure of the anaesthetised cat; their antiacetylcholine and antihistamine activities were also investigated on the response of the blood pressure of cats to intravenous administration of acetylcholine (5 μg) and histamine (5 μg).

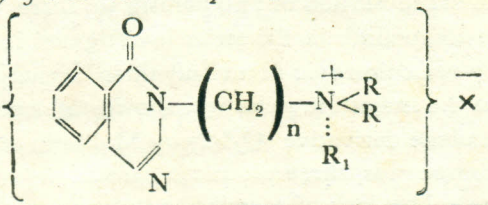
RESULTS

The approximate lethal dose of Q 12 was 75 mg/kg and that for all other compounds was found to be within 150 to 200 mg/kg in mice. The ED_{50} (μg/ml) of the compounds for the antispasmodic activity on guineapig ileum are shown in Table I. In the series studied, only Q8, Q10, Q12 and Q13 were found to have marked antiacetylcholine and antihistamine activity. On further testing of the latter on rabbit ileum only Q13 reduced the normal tone and motility of ileum and to antagonise the effect of barium in concentration ranging from 6 6 to 16·6 μg/ml. Compounds Q10, Q12 and Q13 exerted the negative inotropic effect on the heart at 0·5 mg dose. Compound Q8 produced no change at the corresponding dose and on the contarary, showed the stimulant effect on the heart at higher doses. All of these four compounds caused fall of blood pressure to the extent of 10 to 40 mm of Hg in cats varying with the individual compounds at the intravenous dose level of 1 mg/kg. None of them in the same dose level were appreciably effective in antagonising the fall of blood pressure induced by acetylcholine and histamine in the cat.

TABLE I

Anti-spasmodic activity of 3-substituted-4-quinazolone derivatives

Parent Nucleus :



Code No.	R	R_1	n	X	ED_{50} (μg /ml)	
					Anti-ach.	Anti-hist.
Q1	CH_3	—	2		S	S
Q2	CH_3	CH_3	2	I	10.5	16 6
Q3	CH_3	C_2H_5	2	I	6.6	I
Q4	CH_3	C_3H_7	2	I	I	I
Q5	CH_3	C_4H_9	2	I	S	S
Q6	CH_3	$CH_2CH=CH_2$	2	Br	8.3	16·6
Q7	CH_3	$CH_2C_6H_5$	2	Br	12.1	5·0
Q8	CH_2	$C_2H_4C_6H_5$	2	Br	4.0	10·0
Q9	CH_3	$C_2C_6H_4NO_2$	2	Br	16.6	3·3
Q10	C_2H_5	—	2	—	5.0	1·3
Q11	C_2H_5	CH_3	2	I	6.6	16·6
Q12	C_2H_5	$CH_2C_6H_5$	2	Br	2.5	1·3
Q13	nC_3H_7	—	2	—	4.3	0·5
Q14	nC_3H_7	CH	2	I	I	16·5
Q15	nC_3H_7	$CH_2C_6H_5$	2	Br	9.0	16·5
Q16	nC_3H_7	$CH_2C_6H_4NO_2$	2	Br	I	10 0
Q17	C_4H_9	CH_3	2	I	I	16·5
Q18	C_2H_5	—	3	—	11.0	I
Q19	C_2H_5	CH_3	3	I	10.0	10·0
Q20	3-β-diethylaminoethyl 4-quinazolothione hydrochloride				8.0	3 5
Q21	3-β-γ-dihydroxy propyl-4-quinazolone hydrochloride				I	I

S = Spasmogenic activity at a concentration of 16.6 μg/ml.

I = Failure to show any activity at 16·6 μg/ml concentration.

— = Absence of R_1 and X; compounds tested as hydrochlorides.

DISCUSSIONS

The manifestation of antagonism to three different spasmogens by the effective compounds in the series investigated indicates the non-specific and probably musculotropic nature of their activity. A similar direct relaxant effect on the smooth muscles was shown to be possessed by a 2-3-disubstituted-1-quinazolone derivative (QZ-2) by Malhotra *et al* (1960). Of the four most active compounds, three produced cardiac depression, whereas Q8 showed stimulation. This lack of correlation between antispasmodic and cardiac effects may be ascribed to the difference in the nature (chemical or otherwise) of the compounds. On analysis of the structure-activity relationship of the compounds under investigation, it appears that when the alkyl group attached to tertiary nitrogen is ethyl or propyl as in Q10 and Q13, the overall activity increases ; and in quaternary compounds the N-ethyl substituents seem to have greater influence on the antispasmodic activity than others. In the series of quaternary salts tested, the nature of the radicals used in quaternization appears to be relatively unimportant in determining the type of activity produced. The introduction of sulphur in place of oxygen in quinazolone nucleus diminishes the spasmolytic activity as in Q20. The presence of NO_2 group in the quaternary compounds appears to reduce or abolish the anti-acetylcholine effect while enhancing the antihistamine activity.

The authors are grateful to Dr. B. Mukerji for his interest and encouragement and to Dr. S.N. Pradhan for his valuable criticism in this work. Thanks are also due to Mr. N. Sen for the statistical analysis of the data.

REFERENCES

Bhaduri, A.P., Khanna, N.M. and Dhar, M.L. (1962). *J. Sci. Industr. Res.*, **21 B** (8), 378.

Varma, D.R., Sareen, K.N., Roy, A.K. and Gujral, M.L. (1959). *Ind. J. Physiol. Pharmacol.*, **3**, 168.

Malhotra, J.C., Kohli, R.P., Sareen, K.N., Kishore, K., Amma, M.K.P. and Gujral, M.L. (1960). *Ind. J. Med. Sci.*, **14**, 501.