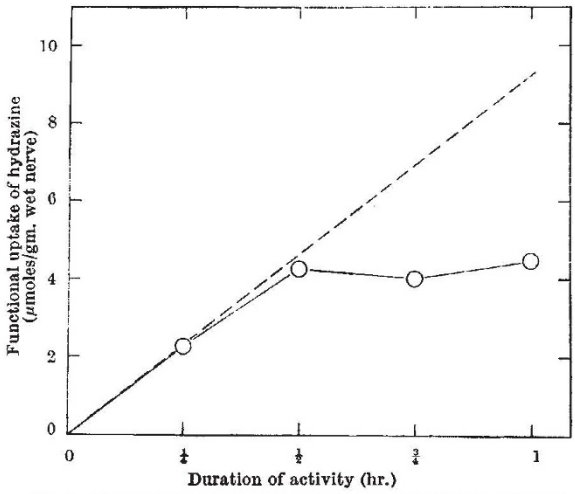

Fig. 1. Functional uptake of hydrazine based on data in Table 2

sodium/hr. activity/gm. wet nerve; a value in agreement with the extrapolated gain in HZ due to activity. The observations suggest that, during activity, HZ replaces sodium quantitatively but is not 'pumped out' as sodium is under normal conditions.

There is no difference between the amounts of protein-'bound' HZ of resting and stimulated nerves. The 'bound' HZ content of 40 nerves was found to be 87·9 ± 33·9 mμmoles/gm.

The extra functional uptake of 4·5 μmoles is only 10 per cent of the initial internal content of 45 μmoles when the nerve was soaked overnight in HZ-Ringer's solution; but apparently is more injurious to nerve activity than the latter. The interpretation of these observations remains, at this moment, obscure. It is not known if the actual maintenance of function by HZ is mediated through a slow release of ammonium ions which cause the nerve to fail irreversibly.

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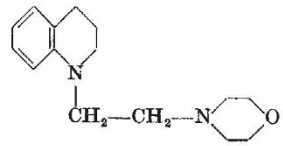
PHARMACOLOGY

New Potent Tetrahydroquinoline Derivative

In connexion with work on tetrahydroquinoline derivatives of medicinal interest, we have recently synthesized a number of alkoxy- and alkyl-substituted 1,2,3,4-tetrahydroquinolines[1] in which various dialkylaminoalkyl groups (carrying in some cases heterocyclic residues such as morpholino, piperidino, etc.) are linked directly to the nitrogen atom. Among the compounds tested so far, *N*-[2-(4-morpholino) ethyl]1,2,3,4-tetrahydroquinoline (I) has shown interesting biological activity.



(I)

Tests carried out with (I) on mice following single oral doses of 126 mgm./kgm. (LD_{50} = approximately 1,000 mgm./kgm.) administered as the hydrochloride demonstrated that (I) significantly elevated the electro-shock-seizure threshold. Elevation of the electro-shock-seizure threshold was of the same order of activity as 2-methyl-3-orthotolyl-4-quinazolone synthesized in this Laboratory[2]. The median protective oral dose of (I) which prevented the extensor phase of electro-shock-induced convulsions in mice was 270 mgm./kgm. of the hydrochloride (95 per cent confidence limits: 225–346 mgm./kgm.). The median protective dose of 2-methyl-3-orthotolyl-4-quinazolone against electro-shock-induced convulsions was 68 mgm./kgm. (95 per cent confidence limits: 51–89 mgm./kgm.). An oral dose of 200 mgm./kgm. did not reduce the conditioned avoidance response in conditioned rats. Mice treated with (I) exhibited ptosis which was reminiscent of reserpine activity. The vasodepressor activity of (I), intravenously applied to acute dog preparations, gave only transitory lowering of blood pressure at a dose-level of 4 mgm./kgm.

Like reserpine[3], (I) antagonizes muscle spasms induced by histamine. On isolated smooth muscle of different species, (I) consistently antagonized acetylcholine effects also. Spasms induced by barium were also reduced by (I) in rat and rabbit ileum, but, in contrast to reserpine, were enhanced in guinea pig ileum. The results obtained indicate that, as far as these preparations are concerned, (I) does not appear to act on specific receptors but may be acting myogenically. This suggestion is supported by the observed ability of (I) to stimulate the nerve-free smooth muscle of chick amnion and the inability of atropine to block the stimulating effects of (I).

Compound (I) was prepared by condensing freshly prepared morpholinoethyl chloride with 1,2,3,4-tetrahydroquinoline. It was distilled as a heavy, pale yellow oil, b.p. 185–188° C. at 3 mm. (found C, 73·35; H, 9·12; N, 11·40; required C, 73·12; H, 9·00; N, 11·37). It is soluble in organic solvents but insoluble in water. For pharmacological screening the hydrochlorides were also prepared: the dihydrochloride, m.p. 166° C. with decomposition (found N, 8·70; required N, 8·77); the monohydrochloride m.p. 203–7° C. (found N, 9·65; required N, 9·87). These salts are freely soluble in water.

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