LETTER TO THE EDITOR

SUBSTITUTED QUINOLINES AS MONOAMINE OXIDASE INHIBITORS AND ANALGESICS

Sir,

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Quinoline derivatives have been shown to possess CNS actvitiy (anticonvulsant and analgesic) and vasodilating properties (1). Hardtmann has reported that 1,4–disubstituted quinoline 2–(1H) ones possess CNS activity (6). 2,3–dihydro–4–quinolines and 1,2,3,4-tetrahydro–4–quinolinols have been shown to possess potent analgesic activity (1, 2). It has been reported that inhibitors of monomine oxidase (MAO) possess pronounced anticonvulsant (4) and analgesic (5) properties. 4–amino quinoline is a potent inhibitor of this enzyme and possesses anticonvulsant properties. On the basis of these observations it was considered desirable to synthesize 8–(β–hydroxy–γ–substituted amino) propoxy quinolines and to evaluate them for their MAO inhibitory and analgesic properties. The steps involved in the synthesis are summarized below (A), (B) and (C).

A. *8–Hydroxy quinoline* –· was prepared following the method reported in the literature (9).

B. *8–(β–γ–epoxy) propyloxy quinoline* – A mixture of 8–hydroxy quinoline (0.5 mole) and epichlorohydrin (1.6 mole) in ethanolic NaOH was stirred at 100°C for 17 hr. The excess of epichlorohydrin was distilled off and the residue was added slowly to water and was stirred, the solid that separated was filtered, washed several times with water and recrystallized with alcohol (mp. 150°C, yield 80%).

C. *8–(β–hydroxy–γ–substituted amino) propoxy quinoline* – 8–(β–γ–epoxy) propyloxy quinoline (1 mole), appropriate secondary amine (3 moles) and alcohol (15 *ml*) were refluxed for 3–4 hr and the solution was concentrated. The mixutre was then diluted with excess of water (100 *ml*) and

boiled on sand–bath until all the excess amine was removed. The solution was cooled, and the product was recrystallized with alcohol. All the compounds were characterized by their sharp melting points, elemental analysis and infra–red spectra (Fig. 1 and Table I).

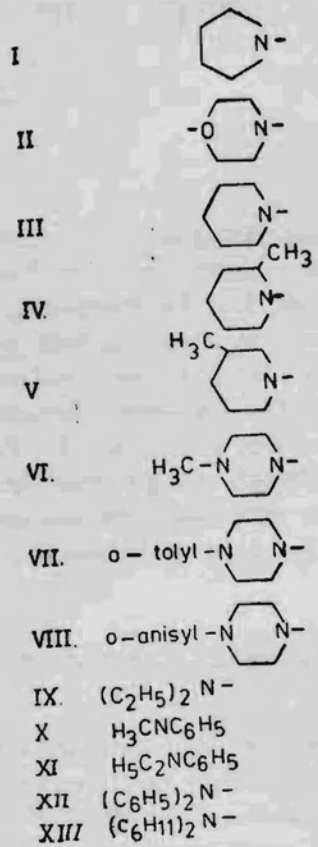


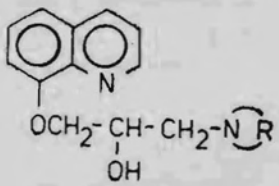
Fig. 1 : Substituted quinolines.
(a) Basic nucleus.
(b) Substituents

The Roman numerals on the left of the figure indicate the compound number.

Monoamine oxidase inhibitory activity :

Adult albino rats (100–150 *g*) were killed by decapitation. Brains were removed and homogenized in ice cold 0.25 *M* sucrose solution. MAO inhibitory activity of the brain

TABLE I : Monoamine oxidase inhibitory and analgesic activity of 8-(β-hydroxy-γ-substituted amino) propoxy quinolines.



Compd. No.	NR	m.p. °C	Molecular formula	MAO inhibition % 2 x 10-4	Analgesic activity	ALD_{50} mg/kg
I		230	$C_{16}H_{20}N_2O_2$	81.30	60	>1000
II		310	$C_{16}H_{20}N_2O_3$	63.10	40	>1000
III		180	$C_{17}H_{22}N_2O_2$	74.40	40	>1000
IV		160	$C_{18}H_{24}N_2O_2$	64.80	60	>1000
V		190	$C_{18}H_{24}N_2O_2$	68.00	60	>1000
VI		310	$C_{17}H_{23}N_3O_2$	64.70	40	>1000
VII		170	$C_{23}H_{27}N_3O_2$	62.00	40	>1000
VIII		195	$C_{23}H_{27}N_3O_3$	62.60	60	>1000
IX		320	$C_{16}H_{22}N_2O_2$	66.50	40	>1000
X		110	$C_{19}H_{20}N_2O_2$	73.00	40	>1000
XI		190	$C_{20}H_{22}N_2O_2$	68.50	40	1000
XII		62	$C_{24}H_{22}N_2O_2$	74.70	40	1000
XIII		140	$C_{21}H_{12}N_2O_2$	68.90	60	>1000

Melting points were determined in open capillary tubes and are uncorrected. Yields were in range of 61–77%. All compounds were analysed for their C, H and N analysis and the values obtained were within ± 0.4% of the theoretical values.

homogenate was determined spectrophotofluorometrically (7) using kynuramine as the substrate. 4–Hydroxy quinoline, formed by the oxidative deamination of kynuramine followed by the spontaneous cyclization of the deaminated product was measured.

The reaction mixture in a final volume of 2.0 *ml* contained 1.0 *ml* phosphate buffer (0.5 *M*, pH 7.4), suitable amount of the enzyme preparation, 20.0 μg of kynuramine

compound to be tested in a final concentration of 2×10^{-4} *M* wandater. The reaction mixture was preincubated for 30 min prior to the addition of the substrate. The reaction was initiated by the addition of the substrate and was terminated after 30 min incubation at 37°C in a water–bath by the addition of 1.0 *ml* trichloroacetic acid (10%, w/v). Proteins precipitated were settled by centrifugation at 700 x g for 10 min. To 1.0 *ml* of the clear supernatant was added 2.0 *ml* of IN NaOH and readings were observed at 315/380 *mμ* using Aminco Bowman Spectrophotofluorometer.

The analgesic activity (acetyl salicylic acid type) of the test compounds was investigated by their ability to protect against a painful writhing syndrome by the method described by Bhalla *et al.* (3). Albino mice of either sex weighing 20–25 *g* were divided into groups of ten, one group of animals was used for each dose of the compound. The test compounds each at a dose of 100 *mg/kg* (ip) were given 3 hr before the induction of aconitine writhing. 2 *μg* of aconitine (100% effective dose) was administered (ip) per mouse. The typical response appeared within 5 min after the injection of aconitine and persisted for about 15–20 min. The mice were observed for 30 min and the results were expressed as percent of mice showing protection (Table I).

In order to obtain an estimate of the toxicity of compounds the approximate LD_{50} (ALD_{50}) values of the compounds were determined following the method of Smith (8).

All the compounds inhibited rat brain monoamine oxidase (62.0–81.3%) and possessed acetylsalicylic acid like analgesic activity. However, as is evident from Table I the analgesic activity of these substituted quinolines was independent of their monoamine oxidase inhibitory activity.

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SUMAN MEHROTRA, J. P. BARTHWAL, T. K. GUPTA AND K. P. BHARGAVA

Jawaharlal Nehru Laboratories of Molecular Biology,
Department of Pharmacology and Therapeutics,
King George's Medical College, Lucknow – 226 003

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