# Some New 2-Methyl-4-[Piperazinylcarbonylethyl/ ethenyl/o-phenylenyl carbonyloxy]-6,7-Substituted Quinolines as Possible Anticonvulsants.

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**Summary:** Twenty four new 2-methyl-4-[piperazinylcarbonylethyl/ethenyl/ o-phenylenylcarbonyloxy]-6,7-substituted quinolines were synthesized by the condensation of 2-methyl-4-hydroxy-6,7-substituted quinoline with piperazinylcarbonyl acid chloride in pyridine. Some of the compounds at a concentration of $1 \times 10^{-3}$ mol/litre inhibited rat brain monoamine oxidase (MAO) in vitro and provided protection against pentylenetetrazole-induced convulsions in mice.

## Introduction

A sizeable number of piperazine derivatives[1-3] possess pronounced anticonvulsant properties. Kishimoto et al. [4] observed that 1-substituted -6,7-dihydroxy-1,2,4-tetrahydro isoquinoline exhibited anticonvulsant and vasodialating properties. 1,4-Substituted quinolin-2-(1H)-ones have been reported to display CNS depressant activity [5], Recently, 3,3-dialkyl-1,2,3,4-tetrahydroquinolines and related Mannich bases were synthesized [6]. All of them were found to possess anticonvulsant activity comparable to that of dilantin. Stimulated by these observations, we synthesized the title compounds as per Scheme-1 with the hope that these compounds might exhibit strong anticonvulsant action.

## Experimental

The structure of the compounds were checked by elemental analysis and I.R. spectra recorded on Perkin-Elmer-157 infracord spectrometer. The purity of the compounds was checked on silica gel G. plates using iodine vapours as visualising agent. The melting points were taken in open capillary tubes and are uncorrected.

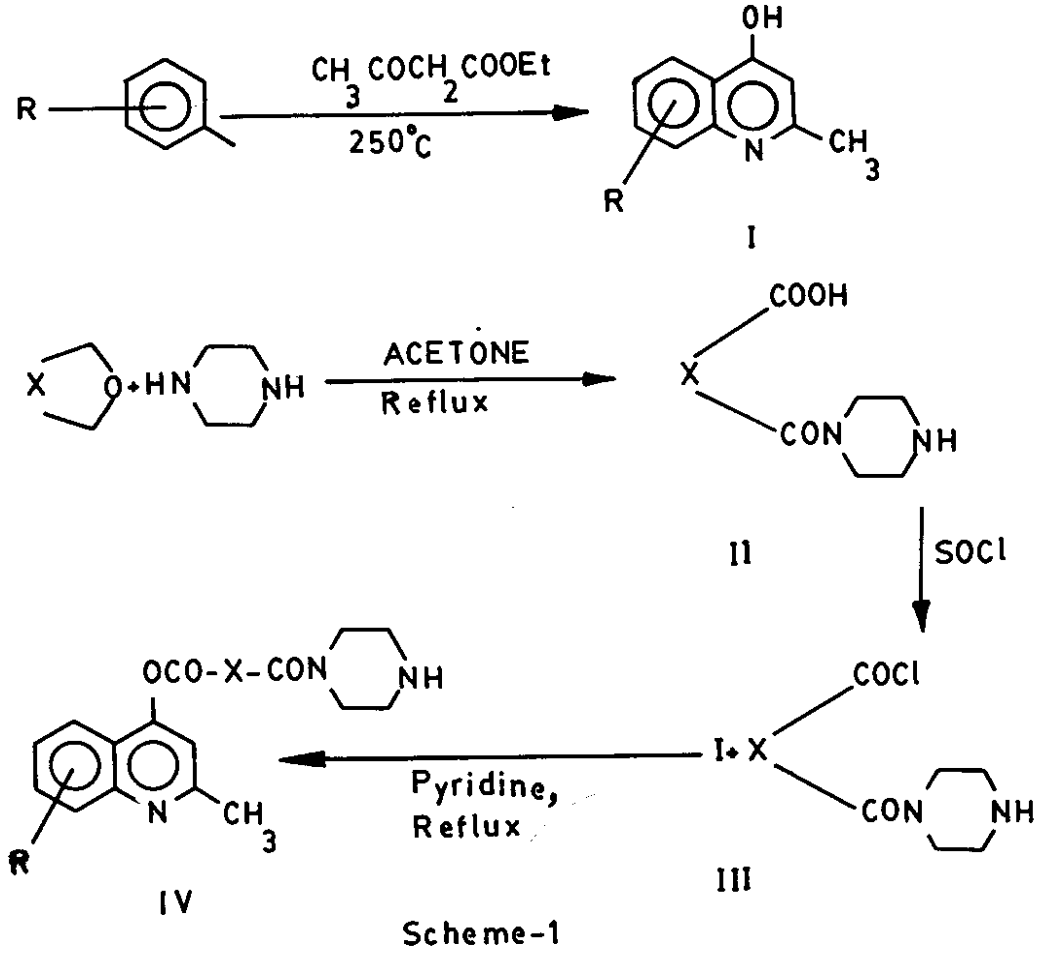
2-Methyl-4-hydroxy-6,7-substituted quinolines (1)[7] and piperazinylcarbonyl-propionic, acrylic and benzoic acids (II)[8] were prepared by the methods available in literature.

*Piperazinylcarbonyl-propionic/ acrylic/benzoic acid chlorides(III):*

Thionyl chloride (0.02 mol) and piperazinylcarbonyl-propionic/acrylic /benzoic acid (0.01 mol) were taken in 100 ml r.b. flask. The mixture was refluxed on a water bath for 2 hours. The excess thionyl chloride was distilled off when the acid chloride was obtained as an oil.

*2-Methyl-4-(piperazinylcarbonylethyl /ethenyl/o-phenylenyl carbonyloxy)-6,7-substituted quinolines (IV):*

2-Methyl-4-hydroxy-6,7-substituted quinoline (0.01 mol), piperazinylcarbonyl-propionic/acrylic/




Scheme-1

benzoic acid chloride (0.01 mol) and pyridine (15 ml) were refluxed on a sand bath for 8 hours. Excess pyridine was distilled off. The residue was poured into ice cold water. The solid obtained was filtered, dried and recrystallised from ethanol (Table-1).

*Biological Studies:*

All the biological studies were carried out on albino mice of either sex weighing 25-30 gms. The number of each group was 10. The compounds were administered at a dose of one-fifth $LD_{50}$ i.p. in form of suspension with gum acacia.

*Effect on gross behaviour:*

The compounds were given intraperitoneally to a group of mice and the behavioural changes were observed. CNS stimulation was judged by increased spontaneous motor activity, piloerection, clonic and tonic convulsion and C.N.S. depression by reduced SMA, sedation, ptoris, reduced muscle tone, loss of righting corneal and pinnal refluxes etc. Depressant action was common among these compounds.

*Monoamine oxidase activity:*

The spectrophotometric method was used for the determination of MAO activity of rat brain homogenate using benzyl amine as substrate [9].

Table-1
2-Methyl-4-(piperazinylcarbonylethyl/ethenyl/o-phenylenylcarbonyloxy)-6,7-substituted quinolines (IV)

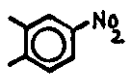
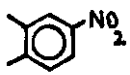
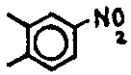
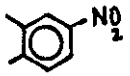
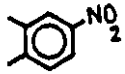
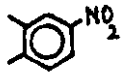
| S.No. | R | X | M.P.°C | Molecular formula | N% Found (Calcd.) | $ALD_{50}$ mg/kg | Gross effect | % protection against pentylene tetrazole-induced convulsions | MAO inhibition % |
|---|---|---|---|---|---|---|---|---|---|
| $IV_1$ | 6-Cl |  | 224 | $C_{22}H_{20}N_3O_3Cl$ | 10.48 (10.26) | 560 | Depressant | 30 | 48.9 |
| $IV_{2*}$ | 7-Cl |  | 220 | $C_{22}H_{20}N_3O_3Cl$ | 10.53 (10.26) | 890 | Depressant | NIL | 78.1 |
| $IV_3$ | 6-Br |  | 246 | $C_{22}H_{20}N_3O_3Br$ | 9.52 (9.25) | - | - | - | - |
| $IV_4$ | 6-$OC_2H_5$ |  | 196 | $C_{24}H_{25}N_3O_4$ | 10.33 (10.02) | 881 | Depressant | NIL | 78.4 |
| $IV_{5*}$ | 6-$OCH_3$ |  | 276 | $C_{23}H_{23}N_3O_4$ | 10.58 (10.37) | 520 | Depressant | 40 | 30.5 |
| $IV_{6*}$ | 6-$CH_3$ |  | 222 | $C_{23}H_{23}N_3O_3$ | 10.99 (10.79) | - | - | - | - |
| $IV_7$ | 6-Cl |  | 228 | $C_{22}H_{19}N_4O_5Cl$ | 12.68 (12.33) | - | - | - | - |
| $IV_8$ | 7-Cl |  | 244 | $C_{22}H_{19}N_4O_5Cl$ | 12.62 (12.33) | 922 | Depressant | NIL | 70.8 |
| $IV_9$ | 6-Br |  | 240 | $C_{22}H_{19}N_4O_5Br$ | 11.48 (11.22) | 1000 | Depressant | 20 | 88.6 |
| $IV_{10}$ | 6-$OC_2H_5$ |  | 226 | $C_{24}H_{24}N_4O_6$ | 12.76 (12.06) | 1000 | Depressant | NIL | 75.6 |

Table-1 cont'd.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $IV_{11}$ | 6-$OCH_3$ |  | 270 | $C_{23}H_{22}N_4O_6$ | 12.73 (12.44) | - | - | - | - |
| $IV_{12}$ | 6-$CH_3$ |  | 228 | $C_{23}H_{22}N_4O_5$ | 12.54 (12.90) | - | - | - | - |
| $IV_{13}$ | 6-Cl | $-CH_2CH_2-$ | 242 | $C_{18}H_{20}N_3O_3Cl$ | 11.91 (11.63) | 480 | Depressant | 20 | 56.2 |
| $IV_{14}$* | 7-Cl | $-CH_2-CH_2-$ | 236 | $C_{18}H_{20}N_3O_3Cl$ | 11.85 (11.63) | 1000 | Depressant | 20 | 56.2 |
| $IV_{15}$ | 6-Br | $-CH_2-CH_2-$ | 228 | $C_{18}H_{20}N_3O_3Br$ | 10.56 (10.34) | - | - | - | - |
| $IV_{16}$* | 6-$OC_2H_5$ | $-CH_2-CH_2-$ | 230 | $C_{20}H_{25}N_3O_4$ | 11.64 (11.32) | - | - | - | - |
| $IV_{17}$ | 6-$OCH_3$ | $-CH_2-CH_2-$ | 222 | $C_{19}H_{23}N_3O_4$ | 11.99 (11.73) | 850 | Depressant | 10 | 72.8 |
| $IV_{18}$ | 6-$CH_3$ | $-CH_2-CH_2-$ | 238 | $C_{19}H_{23}N_3O_3$ | 12.66 (12.31) | 370 | Depressant | 30 | 81.8 |
| $IV_{19}$ | 6-Cl | -CH=CH- | 246 | $C_{18}H_{18}N_3O_3Cl$ | 11.91 (11.69) | - | - | - | - |
| $IV_{20}$* | 7-Cl | -CH=CH- | 244 | $C_{18}H_{18}N_3O_3Cl$ | 11.88 (11.69) | 461 | Depressant | NIL | 54.9 |
| $IV_{21}$ | 6-Br | -CH=CH- | 248 | $C_{18}H_{18}N_3O_3Br$ | 10.53 (10.39) | - | - | - | - |
| $IV_{22}$ | 6-$OC_2H_5$ | -CH=CH- | 222 | $C_{20}H_{23}N_3O_4$ | 11.59 (11.38) | 1000 | Depressant | 20 | 84.6 |
| $IV_{23}$ | 6-$OCH_3$ | -CH=CH- | 224 | $C_{19}H_{21}N_3O_4$ | 12.15 (12.83) | 1000 | Depressant | NIL | 78.4 |
| $IV_{24}$ | 6-$CH_3$ | -CH=CH- | 246 | $C_{19}H_{21}N_3O_3$ | 12.66 (12.38) | - | - | - | - |

Satisfactory (±0.4%) carbon, hydrogen analysis were obtained.

*Showed I.R. spectral bands at 1600 $cm^{-1}$ (C-C aromatic str.), 1620 $cm^{-1}$ -1660 $cm^{-1}$ (N-$\overset{O}{\overset{\|}{C}}$-Str.) 1680 $cm^{-1}$ - 1700 $cm^{-1}$ (O-$\overset{O}{\overset{\|}{C}}$-Str.) and 3400 $cm^{-1}$ (NH Str.).

*Anticonvulsant activity:*

Anticonvulsant activity [10] of the compounds was determined against pentylenetetrazole-induced seizures in mice of either sex weighing 25-30 g. The mice were divided into groups of 10 keeping the group weight approximately the same as far as possible. The test compounds were administered to a group of 10 animals at a dose of 100 mg/kg i.p. Four hours after the administration of these compounds, the mice were injected with pentylenetetrazole (90 mg/kg). This dose of pentylenetetrazole has been shown not only to produce convulsions in almost all untreated mice, but also to exhibit 100% mortality during 24 hour period in control group. An episode of clonic spasm that persisted for at least 5 seconds was considered as threshold convulsion. Animals not exhibiting threshold convulsions during 60 minutes were considered protected. The number of animals protected in each group was recorded and anticonvulsant activity of the substituted quinolines represented as percent protection.

## Results and Discussion

The inhibitory effect of 15 of the synthesized substituted quinolines on monoamine oxidase activity of rate brain homogenate has been recorded. All of them produced 30.5 to 84.6% inhibition of rat brain monoamine oxidase at a final concentration of $1x10^{-3}$ mol/litre. Quinolines having R=6-Br and X=nitro phenyl showed maximum (88.6%) MAO inhibitory effect and that with R=6-O $CH_3$ and X=phenyl showed minimum (30.5%). The anticonvulsant activity of the compounds ranged from 10 to 40% against pentylene-tetrazole induced seizures (Table-1). The compound having R=6-$OCH_3$, X=phenyl showed maximum (40%) protection and with R=6-$OCH_3$, X=-$CH_2$-$CH_2$ - showed minimum (10%) protection. Thus, MAO inhibitory as well as anticonvulsant activity results failed to establish any definite trend in structure-activity relationship.

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## References

1. S.B.Gupta and A.Zie, *Diss.Pharm.Pharmacol.*, **23**, *135 (1971).*
2. V.K.Agarwal, K.C.Sah, S.Nagar and S.S.Parmar, *J.Prakt.Chem.*, **312**, *964 (1970).*
3. A.K.Chaturvedi and S.S.Parmar, *Curr.Sci.*, **41**, *253 (1972).*
4. Kishmoto, Feiji, through *Chem.Abstr.*, **93**, *8338J (1980).*
5. Hardtmann, E.Goctz, through *Chem.Abstr.*, **87**, *135IIId (1977).*
6. A.B. Daruwala, J.E. Gearien, W.J. Dunn, P.S. Benoit, L.J. Bauer, *J.Med.Chem.*, **17**, *819 (1974).*
7. C.R.Hauser and A.E.Reynolds, *J.Amer.Chem.Soc.*, **70**, *2402 (1948).*
8. M.I.Husain, S.N.Misra and M.K. Shukla, *J.Indian Chem.Soc.*, **56**, *171 (1979).*
9. C.W. Tabor, H. Tabor and Rosenphall, *Meth. Enzymol.*, **11**, *39 (1935).*
10. R.P. Kohli, T.K. Gupta, S.S. Parmar and R.C. Arora, *Jap. J. Pharmacol.*, **64**, *881 (1967).*