Effect of 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolones on oxygen uptake in rat brain homogenates containing pyruvic acid[1]

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Selective inhibition of nicotinamide–adenine dinucleotide dependent oxidations of the substrates of the tricarboxylic acid cycle, L-glutamate, and β-hydroxybutyrate by 2-methyl-3-(*o*-tolyl)-4-quinazolone has been reported recently by Parmar and Seth (1). Such quinazolones have been shown to possess hypnotic (2) and anticonvulsant properties (3). Furthermore, in an examination of various naphthoxy ketones for anticonvulsant action, Hunter *et al.* (4) found that 1-acetonyloxy-4-acetylnaphthalene possessed a significantly high therapeutic index in mice. In such naphthoxy ketones the acyl group at position 4 was essential, and lengthening of the alkyl chain decreased their anticonvulsant activity. The ability of several diphenyl pyrrolidinones to affect the central nervous system (5) led us to synthesize 2,3-disubstituted-4-quinazolones from 4′-acetyl-4-aminobiphenyl. In the present study, the effect of substitution in the quinazolone nucleus on pyruvic acid oxidation by rat brain homogenate was investigated.

The quinazolones were synthesized by the reactions shown in Scheme 1 (X and X′ = H, Cl, Br, or I).

EXPERIMENTAL[2]

Synthesis of Anthranilic Acids (I)

The following anthranilic acids (I) were synthesized by the methods reported in the literature: 5-chloroanthranilic acid (6), 5-bromoanthranilic acid (7), 5-iodoanthranilic acid (8), 3,5-dichloroanthranilic acid (6), 3,5-dibromoanthranilic acid (7), and 3,5-diiodoanthranilic acid (8).

Synthesis of Acetanthranils (II)

The acetanthranils (II) were synthesized by refluxing 1 mole of the appropriate anthranilic acid with 2 moles of acetic anhydride for 1 h. After the excess of acetic anhydride was distilled off, the acetanthranils separated as a solid mass and were used without further purification. These acetanthranils were reported earlier (9).

Synthesis of 4′-Acetyl-4-aminobiphenyl (III)

The method described by Misra and Khare (10) was used for the synthesis of 4′-acetyl-4-aminobiphenyl.

Synthesis of Quinazolones (IV)

The quinazolones (IV) were synthesized by heating equimolar proportions of acetanthranils and 4′-acetyl-4-aminobiphenyl as reported earlier (11). The quinazolones shown in Table I were characterized by their melting points and empirical compositions.

Assay of Pyruvic Acid Oxidation by Rat Brain Homogenates

Male albino rats kept on an ad libitum diet were used in all experiments. Rat brains isolated from decapitated animals (100–150 g) were immediately homogenized in a Potter–Elvehjem homogenizer. Rat brain homogenates (25% w/v) were prepared in 0.25 *M* cold sucrose. All incubations were carried out at 37 °C, and the oxygen uptake was measured by the conventional Warburg manometric technique, with air as the gas phase (12). The central well contained 0.2 ml of 20% KOH. The final concentrations of pyruvic acid and 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolones are indicated in Table I. The compounds were dissolved in propylene glycol (100%), and an equivalent amount of the solvent was added to the control vessels.

RESULTS AND DISCUSSION

All of the quinazolones were found to inhibit oxidation of pyruvic acid by rat brain homogenates. The percentage inhibition observed with 2-methyl-3-(*o*-tolyl)-4-quinazolone (38.6 ± 0.5) that was reported earlier (13) was found to increase when 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolone was used (48.5 ± 0.4 (Table I)). Substitution of Cl, Br, and I at position 6 of the quinazolone ring caused a slight increase in the inhibitory power of these carbonyl-containing quinazolones. As is evident from Table I, 6-iodo substituted quinazolone was found to be the most potent compound of this series. The relative electronegativity of the substituents at position 6 may well be a factor affecting the

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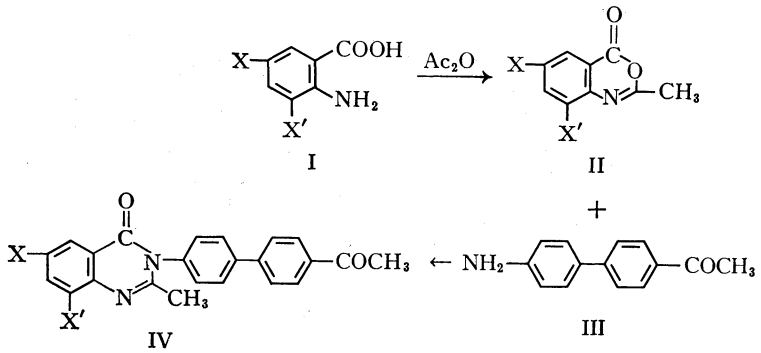
[2]Melting points were determined in a capillary tube and are corrected.



SCHEME 1.

TABLE I

2-Methyl-3-(4′-acetylbiphenyl)-4-quinazolones and their inhibitory effects on pyruvic acid oxidation by rat brain homogenates*

X	X′	Crystallization solvent	Melting point (°C)	Yield (%)	Formula	Carbon (%) Calculated	Carbon (%) Found	Hydrogen (%) Calculated	Hydrogen (%) Found	Nitrogen (%) Calculated	Nitrogen (%) Found	Inhibition (%)
H	H	EtOH	144–146	61	$C_{23}H_{18}N_2O_2$	78.0	77.5	5.1	5.2	7.9	7.7	48.5±0.4
Cl	H	EtOH	188–190	59	$C_{23}H_{17}ClN_2O_2$	71.0	71.1	4.4	4.1	—	—	52.8±0.9
Br	H	EtOH	195–196	57	$C_{23}H_{17}BrN_2O_2$	63.7	63.6	3.9	4.1	—	—	57.4±0.3
I	H	EtOH	199–201	58	$C_{23}H_{17}IN_2O_2$	57.5	58.1	3.5	4.0	5.8	5.5	61.2±0.6
Cl	Cl	AcOH	273–275	57	$C_{23}H_{16}Cl_2N_2O_2$	65.2	65.6	3.8	3.8	—	—	15.0±0.6
Br	Br	AcOH	274–276	55	$C_{23}H_{16}Br_2N_2O_2$	53.9	54.5	3.1	3.7	—	—	30.3±0.8
I	I	AcOH	231–232	55	$C_{23}H_{16}I_2N_2O_2$	45.5	45.1	2.6	3.1	4.6	4.3	15.1±0.1

*All values are the mean of four duplicate experiments. The oxygen uptake was measured at 5 min intervals. The reaction mixture (in a total volume of 3 ml) contained 6.7 m*M* $MgSO_4$, 20 m*M* Na_2HPO_4 in a buffer solution of pH 7.4, 1 m*M* adenylic acid (sodium salt), 33 m*M* KCl, and 500 μg of cytochrome *c*. The oxygen uptake in the control experiment was 46.7–72.1 μl during a 1 h incubation period. The percentage inhibition and standard errors are calculated from the decrease in the oxygen uptake per 125 mg wet weight. The final concentrations of pyruvic acid and 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolones were 10 m*M* and 1 m*M*, respectively.

inhibitory effects of these quinazolone derivatives. Disubstitution at positions 6 and 8 of the quinazolone ring resulted in a decrease in their ability to inhibit pyruvic acid oxidation as compared with unsubstituted or 6-substituted 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolones (Table I). At present it is difficult to provide a suitable explanation for the low inhibitory effects of compounds having substituents at positions 6 and 8 of the quinazolone ring. Our use of purified enzyme preparations in further studies of enzyme inhibition by 2-methyl-3-(4′-acetylbiphenyl)-4-quinazolones in the presence and absence of nicotinamide–adenine dinucleotide may contribute to a better understanding of the biochemical basis of the central nervous system activity exhibited by these hypnotic and anticonvulsant drugs.

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