SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF SOME 4-PHENYL-QUINAZOLINE-2-ONES

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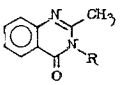
The quinazolines are a group of promising psychotropic agents; Metaqualon (Ia) is used in medicine as a soporific and antispasmodic [1], Lonetil (Ib) has been described by Bulgarian researchers [2-4] as a tranquilizing agent, and some quinazoline-4-one derivatives [5, 6] are reported to have tranquilizing, antispasmodic, and sedative properties. The patent literature [7, 8, 9] contains information on the sedative, anticonvulsive and depressant properties of quinazoline-2-one derivatives. Interestingly, quinazoline-2-ones are formed during the biosynthesis of the 1,4-benzodiazepine series [9, 10].

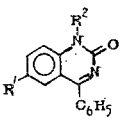


I:a) R = o-$CH_3C_6H_4$
b) R = p-$C_2H_5OC_6H_4$

The present work describes the synthesis and pharmacological properties of the 4-phenylquinazoline-2-ones (II).

Compounds (IIa), (IIi), and (IIj) were prepared as described in [11]. The sulfones (IIj) and (III) were synthesized by the oxidation of (IIf) and (IIh) respectively, using chromium trioxide in glacial acetic acid.

The structures of the previously unreported compounds (IIh), (IIk), and (III) were confirmed by spectral methods [11].



II a): $R^1 = R^2 = H$
II b): $R^1 = Cl$, $R^2 = H$
II c): $R^1 = Br$, $R^2 = H$
II d): $R^1 = CH_3$, $R^2 = H$
II e): $R^1 = Cl$, $R^2 = CH_3$
II f): $R^1 = SCHF_2$, $R^2 = H$
II g): $R^1 = OCHF_2$, $R^2 = H$
II h): $R^1 = SCF_3$, $R^2 = H$
II i): $R^1 = OCF_3$, $R^2 = H$
II j): $R^1 = SO_2CHF_2$, $R^2 = H$
II k): $R^1 = SCHF_2$, $R^2 = CH_3$
II l): $R^1 = SO_2CF_3$, $R^2 = H$

EXPERIMENTAL (BIOLOGICAL)

White mice weighing 18-24 g were used in the following tests of (II) [12]; suppression of convulsions caused by corazole and maximal electroshock, prolongation of barbiturate sleep, loss of motor coordination, and depression of orientation reaction. The tranquilizing action of the most active compounds was determined from the conflict response test on rats [13]. Compounds were injected intraperitoneally. Experimental data (Table 1) showed that the 4-phenylquinazoline-2-ones possessed both corazole antagonism and sedative-hypnotic properties, as shown by the loss of orienting reaction and the prolongation of barbiturate sleep. In the corazole-antagonism test, used in screening for tranquilizers, the quinazolines were less active than chlordiazepoxide (Elenium) but approached Meprobamate and Trioxazine in effectiveness.

Compounds (IIa-e) were evaluated for anticonvulsive activity but even at doses of 1000 mg/kg, they displayed no ability to abolish convulsions caused by maximal electroshock. Disturbance of motor coordination and gait, and other changes of the type caused by a myorelaxant

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TABLE 1. Activity of the 4-Phenylquinazoline-2-ones*

Compound	Corazole antagonism ED_{50}	Disturbance of orientation reaction, ED_{50}	Prolongation of sodium barbiturate sleep, ED_{50}	Loss of motor coordination, ED_{50}	Prevention of convulsions from maximal electroshock, ED_{50}	Toxicity (death of animals), LD_{50}
IIa	5,6 (3,9–8,1)	11,5 (6,6–20,1)	2,2 (1,0–4,0)	≈800	≈800	>800
IIb	10,0 (8,6–11,5)	30,0 (12–75)	—	1000–30 %	1000–10 %	>1000
IIc	5,8 (4,1–8,1)	7,4 (4,6–11,8)	4,0 (2,1–7,6)	>1200	1200	>1200
IId	6,0 (3,9–9,3)	4,0 (1,8–8,0)	2,1 (0,8–5,7)	800–20 %	800–20 %	>800
IIe	≈7,5	50,0 (31,2–80)	—	>150	—	—
IIf	200–16,6 %	50–16,6 % 200–100 %	—	200–16,6 %	50–0 %	>500
IIg	200–0 %	50–100 %	—	200–0 %	50–0 %	>1000
IIh	50–16 %	50–100 %	—	100–0 %	—	—
IIi	100–0 %	100–100 %	—	100–0 %	—	—
IIj	100–16,6 %	100–66,6 %	—	100–0 %	—	—
IIk						100–100 % Convulsions
Chlordiazepoxide	4,6 (3,3–6,4)	13,5 (9,6–18,9)	3,5 (2,4–5,1)	11,8 (10,6–13,1)	17,8 (12,5–23,1)	165 (121.3–224,0)

*ED_{50} is the effective dose in mg/kg, confidence intervals are given in parentheses; in some cases, doses in mg/kg and percentage effect are given.

were produced only on administration of doses exceeding 1000 mg/kg. The toxicity of the 6-halogeno- and 6-methylquinazoline-2-ones was very low; even on injection of 1500 mg/kg, no animals were lost. Quinazolines with fluoro-containing substituents in the 6 position showed less corazole antagonism and caused a decreased loss of orienting reaction compared with compounds (IIa-e). Injection of large doses of (IIf and IIk) caused isolated cases of spasmodic twitching and convulsions.

The 6-halogeno-4-phenylquinazolinones (IIb-c) (25 and 50 mg/kg) like the 1,4-benzdiazepines, exhibit a tranquilizing action, eliminating fear, tension and restlessness in rats in the conflict situation test. Under the influence of these substances, the animals' reaction in the conflict situation was reduced and the drinking reflex normalized.

A comparison of (IIb) and (IIc) with Lonetil [14] showed that although they were less active as tranquilizers in the conflict situation, they had a similar spectrum of pharmacological activity.

The therapeutic range of action of the quinazolinones is greater than that of the corresponding 7-substituted 1,2-dihydro-3H-1,4-benzdiazepine-2-ones [12]. It is interesting to note that in contrast to the latter, there appeared to be no relationship between activity and the electronic configuration of the substituent R^1 for derivatives of 6-phenylquinazoline-2-one. Compounds (IIf), (IIh), and (IIk) might have been expected to have pharmacological properties similar to those of the 6-halogeno-4-phenylquinazoline-2-ones (IIb) and (IIc), since the former has a substituent at position 6 which in its electronic effect on the aromatic ring behaves as a pseudohalogen [15]. However, this is not the case, possibly due either to the bulky fluoro-containing substituents or to specific reactions which occur in biotransformations of compounds (IIf-h) and (IIk).

EXPERIMENTAL (CHEMICAL)

IR spectra of suspensions of the compounds in Nujol were recorded on an IRS-22 spectrophotometer; UV spectra of ethanol solutions were taken on a Specord-UV-VIS spectrophotometer.

6-Trifluoromethylthio-4-phenylquinazoline-2-one (IIh). A solution of 4.2 g (0.01 mole) of 2-trichloroacetylamino-5-trifluormethylthiobenzophenone in 100 ml of a 20% solution of ammonia in ethanol was maintained for 3 days at 20°C, and the solvent and ammonia then distilled off. The solid residue was finely ground, washed with water, alcohol, and ether, and recrystallized from alcohol to give 11 g (38%) of (IIi) with a mp of 228°C. Found, %: C 55.6; H 2.8; F 17.6; N 8.6. $C_{15}H_9F_3N_2OS$. Calculated, %: C 55.9; H 2.8; F 17.7; N 8.7. IR spectrum (ν cm^{-1}): 1610 (C=N), 1660 (C=O), 3376-3126 (NH). UV spectrum, λ_{max} nm (log ε): 204 (4.4); 244 (4.5); 360 (3.5).

6-Difluoromethylthio-4-phenyl-1-methylquinazoline-2-one (IIk). This was prepared in the same way as the previous compound. Yield 58%. Mp 169°C. Found, %: C 60.7; H 3.7; F 12.0; N 8.6. $C_{16}H_{12}F_2N_2OS$. Calculated, %: C 60.4; H 3.7; F 11.9; N 8.8. IR spectrum (ν cm^{-1}): 1610 (C=N), 1660 (C=O). UV spectrum, λ_{max} nm (log ε): 208 (3.8), 264 (3.6), 361 (3.2).

6-Difluoromethylsulfonyl-4-phenylquinazoline-2-one (IIj). To 0.4 g of chromium trioxide in 50 ml of glacial acetic acid 0.36 g (0.0012 mmole) of (IIh) was added with mixing. The mixture was heated on the water bath for 2.5 hours, cooled, and diluted with water. The resulting precipitate was filtered off, washed with water, alcohol, and ether, and dried. Recrystallization from alcohol gave 0.12 g (33%) of (IIj) with a mp of 337-339°C. Found, %: C 54.0; H 2.9; F 11.4; N 8.2. $C_{15}H_{10}F_2N_2O_3S$. Calculated, %: C 53.6; H 3.0; F 11.3; N 8.3. IR spectrum (ν cm^{-1}): 1615 (C=N), 1670 (C=O), 3376-3126 (NH). UV spectrum, λ_{max} nm (log ε): 202 (3.8), 246 (4.3), 272 (4.5), 305 (3.9), 354 (3.2).

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