SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-ACETYL-2,3-DIARYL-1,2,3,4-TETRAHYDROQUINAZOLINE-4-ONES

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UDC 615.2:76.017:615.213]:547.856].012.1

The previously described 2,3-diaryl-1,2,3,4-tetrahydroquinazoline-4-ones [6] represent an interesting trend in the synthesis of biologically active compounds; included among them are compounds having antiinflammatory and anticonvulsive activity [3, 7].

In order to find new 1-acyl-2,3-diaryl-1,2,3,4-tetrahydroquinazoline-4-ones having potential biological activity, and to establish possible relationships between structure and biological activity, we acylated 2,3-substituted 1,2,3,4-tetrahydroquinazoline-4-ones (I) with the corresponding acid anhydrides (II, III), obtaining 1-acetyl(trifluoracetyl)-2-(R'-phenyl)-3-aryl-1,2,3,4-tetrahydroquinazoline-4-ones (IVa-o and VIIa-j) (Tables 1 and 2).

We found that the acylation reaction took place on brief heating of the 2,3-substituted tetrahydroquinazoline-4-ones with acetic or trifluoracetic anhydride, with subsequent neutralization of the reaction products (CH_3COOH, CF_3COOH) with sodium bicarbonate.

The desired products were colorless crystalline substances, insoluble in water, and soluble in ethanol, benzene, dioxane, dimethylformamide, and dimethyl sulfoxide.

The IR spectra of the compounds obtained showed vibrational absorption bands at 1688-1680, 1550-1530, and 1488-1480 cm^{-1}, which may be assigned to quinoline bands, as well as absorption bands in the region of 1512 cm^{-1}, which can be attributed to substitution in the para position. There is no intense band at 3380-3295 cm^{-1} in the IR spectra of the 1-acyl derivatives, which may be explained by the substitution of an acyl radical for a hydrogen atom at position 1.

The PMR spectra of compounds IVa-o, taken in trifluoracetic acid, contained a singlet (triplet) of three methyl protons at 2.35-2.45 ppm, a doublet (quadruplet) of six protons of two methoxy groups at 3.90-3.98 ppm, a doublet (quadruplet) of the two methylene protons of the benzyl radical centered at 4.85-5.0 ppm, and a multiplet of the 11-13 aromatic protons in the three benzene rings centered around 7.23-7.68 ppm. The signal of the CH proton at

TABLE 1. 1-Acetyl(trifluoracetyl)-2-(R'-phenyl)-3-aryl-1,2,3,4-tetrahydroquinazoline-4-ones (IVa-o)

Compound	Yield, %	T_m, °C*	Empirical formula
IVa	63,0	164—6	$C_{25}H_{24}N_2O_4$
IVb	89,0	215—7	$C_{25}H_{24}N_2O_4$
IVc	79,0	158—60	$C_{25}H_{24}N_2O_4$
IVd	92,0	170—72	$C_{25}H_{24}N_2O_5$
IVe	73,0	167—9	$C_{24}H_{21}ClN_2O_4$
IVf	64,2	131—3	$C_{23}H_{20}N_2O_2$
IVg	66,7	157—9	$C_{23}H_{20}N_2O_3$
IVh	48,1	115—7	$C_{23}H_{20}N_2O_3$
IVi	83,7	184—5	$C_{23}H_{19}BrN_2O_2$
IVj	78,8	166—8	$C_{25}H_{24}N_2O_4$
IVk	48,0	167—9	$C_{24}H_{19}F_3N_2O_4$
IVl	86,0	141—3	$C_{25}H_{21}F_3N_2O_4$
IVm	91,0	137—40	$C_{25}H_{21}F_3N_2O_4$
IVn	54,0	158—60	$C_{25}H_{21}F_3N_2O_5$
IVo	91,0	165—6	$C_{24}H_{18}F_3ClN_2O_4$

*Compounds were crystallized from ethanol (IVg, h from benzene).

Perm Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 5, pp. 37-39, May, 1991. Original article submitted June 8, 1990.

0091-150X/91/2505-0305$12.50

TABLE 2. 1-[1-Adamantylacetyl(1-adamantoyl)]-2,3-diaryl-1,2,3,4-tetrahydroquinazoline-4-ones (VIIa-j)

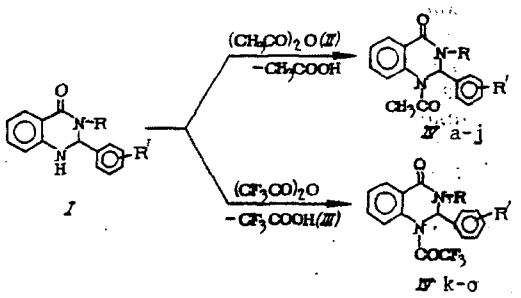
Compound	Yield, %	T_m, °C*	Empirical formula
VII a	59,36	157—8	$C_{35}H_{38}N_2O_5$
VII b	81,0	150—51	$C_{33}H_{34}N_2O_3$
VII c	84,9	138—40	$C_{33}H_{34}N_2O_3$
VII d	49,7	110—13	$C_{34}H_{36}N_2O_3$
VII e	51,3	144—6	$C_{35}H_{38}N_2O_4$
VII f	67,4	146—9	$C_{32}H_{32}N_2O_2$
VII g	52,6	168—70	$C_{32}H_{32}N_2O_3$
VII h	74,3	196—8	$C_{32}H_{32}N_2O_3$
VII i	43,4	174—6	$C_{32}H_{31}BrN_2O_2$
VII j	75,4	167—70	$C_{33}H_{34}ClN_2O_4$

*Compounds were crystallized from benzene.

TABLE 3. Assignment of Absorption Bands in IR Spectra of Compounds VIIIa-j

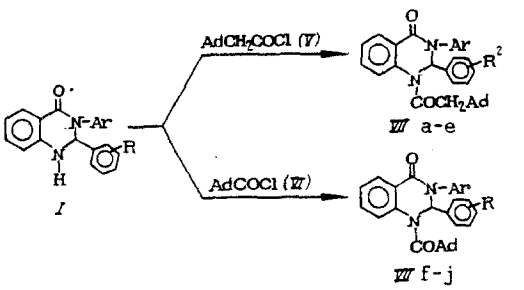
Compound	Vibrations of OH group	Vibrations of Ar(C=O)—N	Quinazolone band 1 and aromaticity	Quinazolone band (C–C bonds in aromatic ring)	Band from vibrations of –C–N<
VII a	—	1675	1610	1480	1328
VII b	3203	1642	1600	1480	1300
VII c	3200	1685	1612	1473	1240
VII d	—	1660	1610	1475	1287
VII e	—	1675	1610	1482	1353
VII f	—	1640	1590	1475	1320
VII g	3408	1630	1582	1482	1384
VII h	3400	1632	1580	1480	1300
VII i	—	1673	1632	1480	1348

position 2 of the quinazolone ring was frequently not seen, since the signals of the aromatic protons were found in that region, which is consistent with the structure assigned to the compounds.



R=2-tolyl(IV a, ℓ), 2-tolyl(IV b), 4-tolyl(IV c,m), 4-anisyl (IV d,n), 4-chlorophenyl(IV e,o), benzyl(IV f-j), H(IV k); R′=2,4-$(OCH_3)_2$ (IV a-e,j-o), H(IV f), 2-OH(IV h), 4-OH(IV g), 4-Br(IV i)

Introduction of the highly lipophilic adamantyl radical into the structure of substances with known pharmacological activity often leads to changes in the strength, duration, and in some cases the nature of the pharmacological activity [4]. For this purpose, 1-(1'-adamantylacetyl)-2,3-diaryl- and 1-(1'-adamantoyl)-2-aryl-3-benzyl-1,2,3,4-tetrahydroquinazoline-4-ones were obtained by acylation of 2,3-substituted tetrahydroquinazoline-4-ones by the corresponding acid chloroanhydrides (V, VI), synthesized according to [5].



Ar=4-anisyl(VII a), benzyl(VII b-i), 4-chlorophenyl(VII j); R= =2,4-$(OCH_3)_2$ (VII a,e,j), 2-OH(VII b,g), 4-OH(VII c,h), 4-OCH_3(VII d), H(VII f), 4-Br(VII i)

It was found that the acylation reaction took place with heating in absolute benzene for 2 h, with a yield of 43-84% (Table 2). The compounds obtained were light-yellow crystalline substances, insoluble in water and soluble in organic solvents (ethanol, dioxane, dimethylformamide, and acetone).

TABLE 4. Antiinflammatory Activity, Anticonvulsant Activity, and Acute Toxicity of Compounds

Compound	Acute toxicity (intraabdominal injection), LD_{50}, mg/kg	Antiinflammatory activity		Anticonvulsant activity		Conditions of pharmacological range, LD_{50}/ED_{50}
		dose tested, mg/kg	increase in foot volume 3 h after injection of agar	peak activity	maximal electroshock test, ED_{50}, mg/kg	
IVd	>5000	100	34,3±4,8 $p<0,02$	—	—	>50
IVe	>5000	100	15,9±3,2 $p<0,001$	—	—	>50
Amidopyrine VIIe	340	100	29,0±4.4 $p<0,01$	—	—	3,4
	840 (718—983)	—	—	5	90 (80—102)	9,3
Hexamidine	240	—	—	240	90 (79—103)	3,7

The structures of the compounds were confirmed by IR spectroscopy. In Table 3, it is apparent that compounds VIIa-j have quinoline bands 1, 2, and 3. These bands are narrow and relatively intense. In addition, the IR spectra display intense bands with a frequency of 1685-1600 cm^{-1}, caused by the ArC=O group.

EXPERIMENTAL (CHEMICAL)

1-Acetyl-2-(2',4'-dimethoxyphenol)-3-(4'-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline-4-one (IVd). To 3.9 g (0.01 mole) 2-(2',4'-dimethoxyphenyl)-3-(4'-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline-4-one was added, with stirring, 10 ml acetic anhydride; this was heated on a boiling water bath for 2 h, after which the reaction mixture was poured into 50 ml of water and neutralized to pH 7 with sodium carbonate. The resulting precipitate was filtered, washed on the filter with 150 ml of water, and crystallized from ethanol. Colorless needles, T_m 170-172°. Yield of IVd: 92%. $C_{25}H_{24}N_2O_5$. IR spectrum, cm^{-1} (Vaseline): 1680 (ArC=O); 1630, 1480 (quinazolone ring); 1512 (p-substitution).

1-Trifluoracetyl-2-(2',4'-dimethoxyphenyl)-3-(4'-chlorophenyl)-1,2,3,4-tetrahydroquinazoline-4-one (IVo). A solution of 3.94 g (0.01 mole) 2-(2',4'-dimethoxyphenyl)-3-(4'-chlorophenyl)-1,2,3,4-tetrahydroquinazoline-4-one in 8 ml of trifluoracetic anhydride was heated on a water bath for 1.5 h. After cooling, the reaction mass was added to 50 ml water and neutralized with sodium carbonate to pH 7. The resulting precipitate was filtered, washed on the filter with 100 ml water, and crystallized from ethanol. Needles with T_m 165-166°. Yield of IVo: 91%. $C_{24}H_{18}F_3ClN_2O_4$.

1-(1'-Adamantylacetyl)-2-(2',4'-dimethoxyphenyl)-3-(4'-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline-4-one (VIIa). To a solution of 3.9 g (0.01 mole) 2-(2',4'-dimethoxyphenyl)-3-(4'-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline-4-one in 30 ml absolute benzene was added dropwise, with stirring, a solution of 2.1 g (0.01 mole) of 1-adamantaneacetic acid chloroanhydride in 10 ml absolute benzene; this was stirred for 1 h. The precipitate which formed following cooling was filtered and crystallized from benzene. Light-yellow prisms, T_m 157-158°. Yield of VIIa: 59.36%. $C_{35}H_{38}N_2O_5$. IR spectrum, cm^{-1} (Vaseline): 1673, 1618, 1558, 1477, 1308, 1268. The data from elemental analysis of the compounds agreed with calculated values.

EXPERIMENTAL (BIOLOGICAL)

Compounds IV and VII were studied for the presence of antiinflammatory activity, using the model of agar inflammation in the rat, and for anticonvulsive activity with the maximal electroshock test.

Acute toxicity of the compounds was determined by intraabdominal administration in a 2% starch gel.

Pharmacological screening showed that the greatest biological activity was possessed by those compounds containing a 2',4'-dimethoxyphenyl radical at position 2 of the quinazolone ring [1, 2].

Hence, 1-acetyl-2-(2',4'-dimethoxyphenyl)-3-[(4-methoxyphenyl) or (4-chlorophenyl)]-1,2,3,4-tetrahydroquinazoline-4-ones showed the greatest antiinflammatory activity, using the model of agar inflammation in white rats [2].

The greatest anticonvulsant activity in the maximal electroshock test was displayed by 1-adamantylacetyl-2-(2',4'-dimethoxyphenyl)-3-benzyl-1,2,3,4-tetrahydroquinazoline-4-one [1] (Table 4).

All compounds studied were found to have low toxicities, with the LD_{50} ranging from 600 to greater than 5000 mg/kg.

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