SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-SUBSTITUTED 2-CYCLOALKYLQUINOLINES

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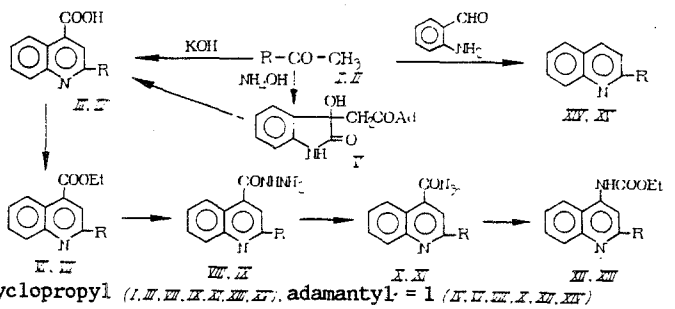
2-R'-4-R-quinolines are known to possess high biological activity, and they have found application in medicine [3]. Some hydrazides, acylazides, and urethanes of 2-aryl (and hetaryl)quinoline-4-carboxylic acids display antiviral and antibacterial activity [1, 2]. Some 4-adamantylaminoquinolines have also been found to possess antimalarial and antiprotozoal activity [4].

Continuing work on the synthesis and examination of the biological activity of 2-R'-4-R-quinolines, it was considered desirable to develop convenient methods for the synthesis of 2-cycloalkylquinoline-4-carboxylic acids and their derivatives. In this connection, it was of importance to establish the influence of a cycloalkyl substituent in the 2-position of the quinoline ring on biological activity. This made it possible to compare the properties and biological activity of aryl, hetaryl, and cycloalkylquinolines.

The 2-cycloalkylquinolines were obtained as follows:



R = cyclopropyl (I, II, III, IX, X, XIII, XIV), adamantyl- = 1 (IV, V, VI, X, XI, XII)

4-Carboxyquinolines are usually obtained by the Pfitzinger reaction between isatin and the appropriate methyl ketones in basic media. However, this method gave good yields only with 2-cyclopropyl-4-carboxyquinoline (III). The yield of 2-(1-adamantyl)-4-carboxyquinoline (IV) was 5-10%. This appears to be due to steric hindrance caused by the steric structure of the adamantyl ring [5]. It was possible to obtain (IV) by isolating the intermediate 3-hydroxy-3-(1-adamantyl)carbonylmethyloxindole (V), which on heating in the minimum amount of a mixture of sulfuric and acetic acids gave (IV) in 94% yield [1].

The derivatives (VI-XIII) were obtained from the acids (III) and (IV).

Condensation of the methyl cycloalkyl ketones (I) and (II) with o-aminobenzaldehyde (the Friedlander reaction) gave 2-(1-adamantyl)quinoline (XIV) and 2-cyclopropylquinoline (XV).

The purity and structures of the products were confirmed by their elemental analyses and IR spectra (Table 1).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a Spectromom-200 spectrophotometer, in KBr disks.

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TABLE 1. 2-R'-4-R-Quinolines

Compound	R	R'	Yield, %	mp, °C	Empirical formula	IR spectrum, ν, cm^{-1}			Minimum bacteriostatic or mycostatic concentration, μg/ml		
						CO	NH	N_3	Staph. aureus 209P	E. coli 675	Microsporum canis (Janosum)
III	COOH	cycloPr	84	195—6	$C_{13}H_{11}NO_2$	1708			>200	>200	200
IV	COOH	Ad-1	94	277—9	$C_{20}H_{21}NO_2$	1718			200	>200	25
VI	$COOC_2H_5$	Ad-1	58	75—6	$C_{22}H_{25}NO_2$	1720			>200	>200	>200
VII	$COOC_2H_5$	cycloPr	52	32—3	$C_{15}H_{15}NO_2$	1745			>200	>200	25
VIII	$CONHNH_2$	Ad-1	98	146—7	$C_{20}H_{23}NO$	1630	3200				
IX	$CONHNH_2$	cycloPr	84	200—2	$C_{13}H_{13}NO$	1620	3170		>200	>200	>200
X	CON_3	Ad-1	63	200 (decomp.)	$C_{20}H_{20}N_4O$	1700		2250	1,56	>200	>200
XI	CON_3	cycloPr	89	58 (decomp.)	$C_{13}H_{10}N_4O$	1680		2170	>200	>200	100
XII	$NHCOOC_2H_5$	Ad-1	62	146—8	$C_{22}H_{26}N_2O_2$	1745	3100		25	>200	50
XIII	$NHCOOC_2H_5$	cycloPr	67	140—2	$C_{15}H_{11}N_2O_2$	1700	1600		>200	>200	>200
XIV	H	Ad-1	75	92—5	$C_{19}H_{21}N$				>200	>200	>200
XV	H	cycloPr	87	63—4	$C_{12}H_{11}N$				>200	>200	>200

2-Cyclopropyl-4-carboxyquinoline (III). A mixture of 8.4 g (0.1 mole) of methyl cyclopropyl ketone (I), 14.1 g (0.096 mole) of isatin, 21.1 g of potassium hydroxide, 11.2 ml of ethanol, and 54 ml of water was boiled for 5-7 h. After cooling, the solution was acidified with hydrochloric acid until weakly acid, and the solid which separated was filtered off, washed with water, and dried to give 17.89 g (84%) of product.

3-Hydroxy-3-[(1-adamantyl)carbonylmethyl]oxindole (V). A mixture of 10 g (0.056 mole) of methyl 1-adamantyl ketone (II) and 8.6 g (0.059 mole) of isatin in 140 ml of ethanol and 14 ml of aqueous ammonia was heated to the boiling point (but not boiled), then kept at ambient temperature for one day. The crystals which separated were filtered off, washed with aqueous alcohol, and dried to give 15.5 g (84%) of (V), mp 245-246°C. Found: N 4.2%. $C_{20}H_{23}NO_3$. Calculated: N 4.3%. IR spectrum: 1620 cm^{-1} (CO), 3300 cm^{-1} (OH).

2-(1-Adamantyl)-4-carboxyquinoline (IV). To a mixture of 37 ml of acetic acid, 44 ml of water, and 18.5 ml of concentrated sulfuric acid was added 4.1 g (0.013 mole) of the oxindole (V), and the mixture boiled with stirring for 3-5 h. After keeping at ambient temperature for one day, the crystals which separated were filtered off, washed with water, and dried to give 3.65 g (94%) of (IV).

2-(1-Adamantyl)-4-ethoxycarbonylquinoline (VI). To a solution of 6 g (0.0195 mole) of (IV) in 150 ml of ethanol was added dropwise 20 ml of concentrated sulfuric acid, and the mixture boiled for 15 h. It was then cooled, neutralized with cooling with saturated sodium bicarbonate solution, and the solid which separated was filtered off and dried to give 63.77 g (58%) of (VI).

2-Cyclopropyl-4-ethoxycarbonylquinoline (VII) was obtained similarly.

2-(1-Adamantyl)-4-hydrazidoquinoline (VIII). A mixture of 1.3 g (0.0039 mole) of (VI), 12 ml of ethanol, and 2.6 ml (0.053 mole) of 85% hydrazine hydrate was boiled for 3 h, cooled, diluted with water, and the solid which separated filtered off. Yield 1.23 g (98%).

2-Cyclopropyl-4-hydrazidoquinoline (IX) was obtained similarly.

2-(1-Adamantyl)-4-acylazidoquinoline (X). To a solution of 1.23 g (0.0038 mole) of (VIII) in 40 ml of water and 10 ml of concentrated sulfuric acid was added dropwise with stirring at 2-3°C a solution of 6.9 g (0.1 mole) of sodium nitrite in 50 ml of water. The mixture was kept for 2 h at this temperature, then the solid which separated was filtered off and dried to give 0.8 g (63%) of (X).

2-Cyclopropyl-4-acylazidoquinoline (XI) was obtained similarly.

2-(1-Adamantyl)-4-ethoxycarbonylaminoquinoline (XII). A solution of 0.75 g (0.0023 mole) of (X) in 25 ml of absolute alcohol was boiled for 3 h, and kept at ambient temperature. The solid which separated was filtered off to give 0.49 g (62%) of (XII).

2-Cyclopropyl-4-ethoxycarbonylaminoquinoline (XIII) was obtained similarly.

2-(1-Adamantyl)quinoline (XIV). A mixture of 0.9 g (0.005 mole) of (II), 0.6 g of o-aminobenzaldehyde, 15 ml of ethanol, and a catalytic amount of potassium hydroxide was boiled for 1 h. The mixture was then cooled, diluted with water, and the solid which separated filtered off, washed with water, and dried to give 1 g (75%) of (XIV).

2-Cyclopropylquinoline (XV) was obtained similarly.

EXPERIMENTAL (BIOLOGY)

The antimicrobial activity of the compounds obtained was determined by double serial dilution in a liquid nutrient medium (Hottinger's bouillon for bacteria, and Sabouraud's medium for the fungus). The compounds were dissolved in dimethyl sulfoxide, the diluted with the appropriate medium. The test strains used were *Staphylococcus aureus* 209P, *Escherichia coli* 675, and the fungal dermatophyte *Microsporum canis*. The inoculum for bacteria was $2.5 \cdot 10^5$ microbial cells per ml, and for the fungus, $5 \cdot 10^5$ microbial cells per ml. The maximum concentration used was 200 μg/ml.

As will be seen from Table 1, none of the 2-cyclopropylquinolines showed (III, VII, IX, XIII, XV) antibacterial activity against *S. aureus* 209P or *E. coli* 675. Activity was shown against *M. canis*, depending on the substituent in the 4-position of the quinoline ring, which was moderate in (VII) and weak in (III) and (XI) (the substituent being ethoxycarbonyl, carboxy, or acylazido respectively). Compounds (XIV) and (XV) were devoid of antimicrobial activity.

In the 2-(1-adamantyl)-substituted quinolines, the type and level of activity varied depending on the substituent in the 4-position of the quinoline ring. For example, the carboxy group in (IV) led to the appearance of moderate antifungal and weak antistaphylcoccal activity. Replacement by the ethoxycarbonyl group (VI) resulted in the loss of antimicrobial activity, while the ethoxycarbonylamino residue conferred antimicrobial activity (moderate antistaphylococcal and antifungal) on (XII). The acylazide radical in (X) conferred high antibacterial activity against *S. aureus* 209P. The oxindole (V) showed moderate antifungal activity.

Hence, 2-cycloalkylquinolines bearing an adamantyl radical are generally more active as antimicrobials than the cyclopropyl compounds, especially in conjunction with acylazide, carboxyl, and ethoxycarbonylamino substituents.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF CINNAMIC ACID DERIVATIVES

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The detection of high levels of viricidal activity in β-naphthoquinones [3] and antiviral activity in sulfamoylbenzoic acids [7], their complex esters [8] and amides [9] as well as in derivative acrylic acids [5] has indicated that this type of research holds promise in the series of sulfamoylnapthoquinones and sulfamoylcinnamic acids as well. In that connection we synthesized 1-nitroso-2-naphthol containing a 6-sulfamoyl (III, IV) group or a 6-benzoyl (XI) group and split them into o-cyanocinnamic acids (V, VIII, XII). For our biological testing as described in [4, 10, 11] we also synthesized substituted 1-nitroso-2-naphthols (XV-XIX), cinnamic acids (XX-XXVIII) and their derivatives (XIII, XIV, XXIX-XXXVI).

The starting compounds 6-sulfamoyl-2-naphthol (I) and 6-(dimethylsulfamoyl)-2-naphthol (II) were obtained through the chloroanhydride of the corresponding sulfonic acid with protection of the hydroxyl group. In their UV-spectra the bathochromatic shifts were maximal in comparison to the spectra of 2-naphthol [1], although a typical phenol shift was observed in an alkaline medium. Nitration of I and II $NaNO_2$ proceeded smoothly in diluted AcOH and resulted in stable 1-nitroso-2-naphthols III and IV. The same characteristics as exhibited in the non-substituted 1-nitroso-2-naphthol [10] were manifested in their spectra in ethanol, acid, and base media.

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