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SYNTHESIS OF POTENTIAL ANTAGONISTS TO AMINO ACIDS IN THE QUINOLINE SERIES

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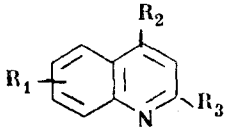
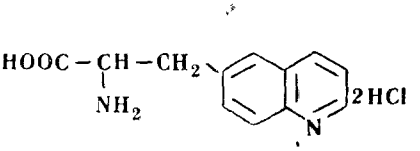
The following potential antagonists to amino acids were synthesized: β-(6-quinolyl)-α-alanine, β-(8-quinolyl)-α-alanine, and β-(2-phenyl-4-carboxy-6-quinolyl)-α-alanine.

In recent years there has been a considerable increase in interest in potential antimetabolites, and numerous analogs of amino acids, vitamins, and other metabolites [1-3] have been synthesized. Derivatives of various heterocycles-thiophene [4], quinoline [5, 6], acridine [7], phenanthroline [8], etc., have been prepared as antagonists to amino acids.

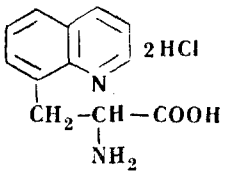
This paper describes the synthesis of quinoline-containing potential antagonists having the general formula I.



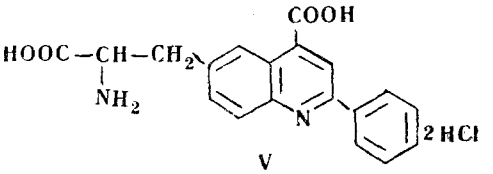
I



II



III



V

β-(6-Quinolyl)-α-alanine dihydrochloride (II) and β-(8-quinolyl)-α-alanine dihydrochloride (III) were prepared by hydrolyzing the corresponding acetylamino malonic ester derivatives (IVa, b), which in turn were synthesized from halogenomethylquinolines and acetylaminomalonic ester. The method previously described for preparation of 6-chloromethylquinoline [9] was not used. Instead it was prepared by reacting 6-quinolylcarbinol[10] and thionyl chloride, the yield being about 80%. Bromination of 8-methylquinoline with bromosuccinimide in the presence of benzoyl peroxide gives 8-bromomethylquinoline [11-12]. β-(2-Phenyl-4-carboxy-6-quinolyl)-α-alanine dihydrochloride (V) was isolated by hydrolysis of VI, prepared by the Doebner reaction by reacting p-aminobenzylacetylaminomalonic ester, benzaldehyde, and pyrotartaric acid.

The quinolylalanines II, III, and V give a positive ninhydrin reaction. Some properties of the compounds prepared are given in the table.

EXPERIMENTAL

6-Chloromethylquinoline. 2.6 g 6-quinolylcarbinol and 30 ml dry chloroform are placed in a flask fitted with a stirrer, a reflux condenser with a calcium chloride tube, and a dropping funnel. 15 ml thionyl chloride are dropped in, and the mixture boiled for 2 hr. The chloroform and thionyl chloride are distilled off in a vacuum, chloroform being added twice and each time distilled off. The 6-chloromethylquinoline hydrochloride (m.p. 181-183°) is dissolved in water, the base liberated with alkali, filtered off, washed with water, and dried. 2.26 g (78%) 6-chloromethylquinoline are obtained, m.p. 69-70° ([9] gives m.p. 68-70°).

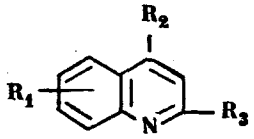
Ethyl β-(6-quinolyl)-α-(carbethoxy)-α-N-acetylaminopropionate (IVa). 0.33 g sodium is added to 16 ml anhydrous alcohol, and when it has dissolved, 3.15 g acetylaminomalonic ester is added. The mixture is boiled 15 min and cooled, and 2.5 g 6-chloromethylquinoline is added. After boiling for 2 hr the reaction mixture is cooled, the precipitate filtered off, washed with water, and dried. Recrystallization from 30% alcohol gives 2.8 g (56%) of colorless crystals of VIa.

Ethyl β-(8-quinolyl)-α-(carbethoxy)-α-N-acetylaminopropionate (IVb). Prepared similarly to IVa.

Ethyl β-(2-phenyl-4-carboxy-6-quinolyl)-α-(carbethoxy)-α-N-acetylaminopropionate (VI). A mixture of 17 g p-aminobenzylacetylaminomalonic ester, 5.8 g benzaldehyde, and 60 ml anhydrous alcohol is refluxed for 30 min. The reaction mixture is cooled, 4.8 g pyrotartaric acid added, and the mixture refluxed 2 hr. It is then placed in a refrigerator to crystallize, the precipitate filtered off, washed, and crystallized from alcohol, to give 3 g (11.9%) of VI.

β-(6-Quinolyl)-α-alanine dihydrochloride (II). 5.5 g IVa and 72 ml 20% hydrochloric acid are boiled together for

TABLE



Compound	Position R_1	R_1	R_2	R_3	Yield, %	M.p., °C	Empirical formula	Elementary analysis, %							
								C		H		Cl		N	
								Found	Calculated	Found	Calculated	Found	Calculated	Found	Calculated
II	6	$CH_2—CH(NH_2)—COOH$	H	H	65	>250 (hydrochloric acid-alcohol)	$C_{12}H_{12}N_2O_2 \cdot 2HCl$	49.50 49.53	49.82	4.66 4.88	4.84	24.14 25.03	24.56	9.22 9.54	9.69
III	8	$CH_2—CH(NH_2)—COOH$	H	H	51.5	235–236 (hydrochloric acid-alcohol)	$C_{12}H_{12}N_2O_2 \cdot 2HCl$	50.20 50.37	49.82	4.45 5,09	4.84	24.77 24.77	24.56	9.50 9.28	9.69
IVa	6	$CH_2—C(NHCOCH_3)(COOC_2H_5)_2$	H	H	56	156 (30% alcohol)	$C_{19}H_{22}N_2O_5$	63.64 63.95	63.69	5.95 6.15	6.15	—	—	7.96 7.80	7.82
IVб	8	$CH_2—C(NHCOCH_3)(COOC_2H_5)_2$	H	H	47	112–114 (30% alcohol)	$C_{19}H_{22}N_2O_5$	63.63 63.65	63.69	6.07 6.03	6.15	— —	— —	8.07 8.02	7.82
V	6	$CH_2—CH(NH_2)—COOH$	COOH	C_6H_5	38.2	>250 (hydrochloric acid-alcohol)	$C_{19}H_{16}N_2O_4 \cdot 2HCl \cdot 2H_2O$	51.66	51.23	4.65	4.94	15.83 15.62	15.95	6.43 6.16	6.29
VI	6	$CH_2—C(NHCOCH_3)(COOC_2H_5)_2$	COOH	C_6H_5	11.9	222 (alcohol)	$C_{26}H_{26}N_2O_7$	—	—	—	—	—	—	6.04 6.10	5.85

4 hr. After the volatile components have been vacuum distilled, the residue is dissolved by small portions in hot hydrochloric acid, which is then cooled, and twice the volume of alcohol added. On rubbing the walls of the vessel colorless material is precipitated; this is filtered off, washed with alcohol, and dried, giving 2.9 g (65%) of II. The base prepared from II by the action of triethylamine melts at 246-247°.

β-(8-Quinolyl)-α-alanine dihydrochloride (III). Prepared similarly to II.

β-(2-Phenyl-4-carboxy-6-quinolyl)-α-alanine dihydrochloride (V), dihydrate. Prepared similarly to II.

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INVESTIGATIONS OF SYNTHETIC DYES. XLV. STYRYLS FROM N-ARYLQUINALDINE SALTS

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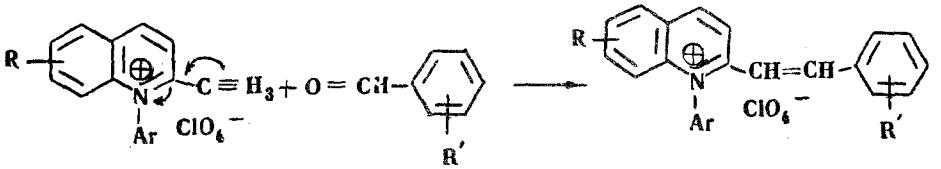
Condensation of N-arylquinaldine salts with benzaldehyde and its o- and p-derivatives gives a series of styryl compounds. The absorption maxima of the hydroxystyryls are bathochromically shifted by 12-34 mμ, as compared with the unsubstituted analogs. Transformation of hydroxystyryl salts to the bases is linked with deepening of the color by 90-130 mμ.

The relative mobility of the methyl hydrogens of N-halogenarylates of quinaldine, due to conjugation of the group with a cationic center, causes onium salts to condense rather readily with aromatic aldehydes. Continuing research along these lines, we used benzaldehyde and its o- and p-hydroxy derivatives for the condensation. The starting salts were synthesized by cyclizing the corresponding secondary aromatic amines with acetaldehyde in acid medium using methods previously developed [1, 2].



The spectra of the dyes prepared (table) were observed in acid and alkaline 96% alcohol.

Compounds I-XIII are comparatively highly colored, and have low molecular extinctions. Their absorption bands lie in a narrow range of long wavelengths, and the change in structure of the quinoline ring affects their light absorption to only an insignificant extent. A hydroxy group in the o position of the N-phenyl ring (I and II, V and VI) causes a small hypsochromic displacement of the absorption maximum, while an acetoxy group causes a smaller effect in the same direction (I and III, V and VII). The effect of these same groups in the p position of phenyl is somewhat weaker, and the absorption maxima of compounds V and VIII almost coincide. These facts correspond to the action of the OH