QUINAZOLINES

VIII.* REACTION OF 2-AMINO-4-QUINAZOLONE WITH UNSATURATED ACIDS

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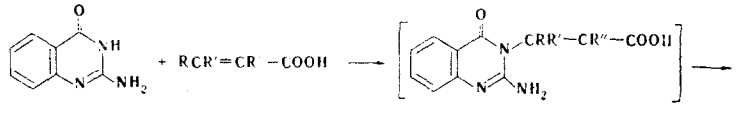
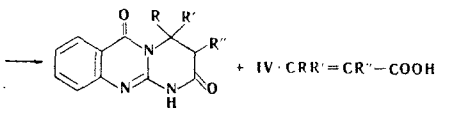
The reaction of 2-amino-4-quinazolone with unsaturated acids such as acrylic, methacrylic, dimethylacrylic, crotonic, and cinnamic acids was studied, as a result of which the previously undescribed 1,2,3,4-tetrahydropyrimido[2,1-b]quinazoline-2,6-diones were synthesized.

It is known that 1,2,3,5-tetrahydroimidazo[2,1-b]quinazolines [2] have a broad spectrum of biological activity. In order to search for new pharmacologically active substances and to continue our research on the synthesis of quinazolines we studied the reaction of 2-amino-4-quinazolone with unsaturated acids such as acrylic, methacrylic, dimethylacrylic, crotonic, and cinnamic acids.



I IIa-e IIIa-e

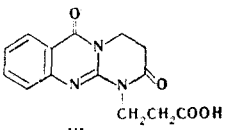


IVa-e Va-e

II-V a R = R′ = R″ = H; b R = R′ = H, R″ = CH_3; c R = CH_3, R′ = R″ = H; d R = R′ = CH_3, R″ = H; e R = C_6H_5, R′ = R″ = H

1,2,3,4-Tetrahydropyrimido[2,1-b]quinazoline-2,6-diones (IVa-e, Table 1) were obtained in good yields as a result of this study; we were unable to isolate intermediates IIIa-e.

The reaction takes place when equimolar amounts of amine I and acid II are refluxed in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), and the products are obtained in 40-50% yields; however, better results are obtained when the starting reagents are fused at 160-165°C. In addition to the principal products (IVa-e), small amounts of salts formed between IV and the starting acid (V) were isolated from the reaction mixtures. 1-(β-Carboxypropyl)-1,2,3,4-tetrahydropyrimido[2,1-b]quinazoline-2,6-dione (VI), which is the product of the addition of a second molecule of acid IIa to pyrimidoquinazolinedione IVa, is formed when a twofold excess of acrylic is used.



VI

To prove the structure of IVa-e we accomplished the alternative synthesis of pyrimidoquinazolinedione IVa from the sodium salt of 2-amino-4-quinazolone and 3-chloropropionic acid. Since the alkylation of salts of

*See [1] for communication VII.

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TABLE 1. 1,2,3,4-Tetrahydropyrimido[2,1-b]quinazoline-2,6-diones

Compound	mp, °C[a]	Found, %			Empirical formula	Calc., %			M		Yield, %
		C	H	N		C	H	N	found[b]	calc.	
IVa	250	61,5	4,3	19,3	$C_{11}H_9N_3O_2$	61,3	4,2	19,5	215	215,2	61
VI	208—210	58,7	4,7	14,8	$C_{14}H_{13}N_3O_4$	58,5	4,5	14,6	287	287,2	75
IVb	274—275	63,0	5,0	18,4	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	229	229,2	75
IVc[c]	—	63,0	4,9	18,1	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	229	229,2	80
IVd	206	64,0	5,6	17,4	$C_{13}H_{13}N_3O_2$	64,2	5,4	17,3	—	243,2	73
IVe	268—269	70,3	4,7	14,1	$C_{17}H_{13}N_3O_2$	70,1	4,5	14,4	291	291,3	90

[a]The compounds were purified by recrystallization from alcohol. [b]Determined by mass spectrometry. [c]Sublimes at 290°C.

2-amino-4-quinazolone by alkyl halides takes place at the nitrogen atom in the 3 position of the pyrimidine ring [3], the formation of IVa via this pathway refutes other alternative structures for the products of the reaction of amine I with acids IIa-e.

Absorption bands at 1635-1690 (C=O) and 3400 cm^{-1} (NH) are present in the IR spectra of IVa-e. The PMR spectral data also confirm the structures of the products. Thus signals of protons of methylene groups in the 3 and 4 positions of the system are observed in the spectrum of IVa at 3.9-4.4 and 2.5-2.8 ppm; the protons of the aromatic ring give a multiplet signal at 7.0-7.5 ppm. The mass spectra of IVa-e contain a molecular ion peak of moderate intensity (15-50%); the most intense peak is the ion peak with m/e 161 (50-100%).

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 mass spectrometer. The PMR spectra of solutions of the compounds in d_5-pyridine were recorded with a JNM-44-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer.

2-Amino-4-quinazolone (I). This compound was synthesized by an improved method [4]. A mixture of 24 g (300 mmole) of calcium cyanamide, 40 ml of water and 40 ml of concentrated hydrochloric acid was stirred at room temperature for 1 h, after which it was filtered. A solution of 8.2 g (60 mmole) of anthranilic acid in 60 ml of water and 8 ml of concentrated HCl was added to the filtrate, and the mixture was heated with stirring on a water bath at 85-90°C for 1.5 h. It was then cooled and made alkaline with ammonia, and the precipitated crystals were removed by filtration, washed with water, dried, and crystallized from alcohol to give 8.65 g (91%) of amine I with mp 315°C (in agreement with the data in [4]).

1,2,3,4-Tetrahydropyrimido[2,1-b]quinazoline-2,6-dione (IVa). A) A mixture of 0.7 g (4.3 mmole) of amine I and 0.3 g (4.1 mmole) of acrylic acid was fused at 160-165°C for 2 h, after which it was cooled and treated with water. The precipitated crystals were separated, dried, and crystallized from alcohol to give 0.54 g of IVa. IR spectrum: 1635, 1690 (C=O); 3400 cm^{-1} (NH).

The filtrate from the separation of IVa was evaporated to dryness, and the residue was crystallized from alcohol to give 0.1 g of salt Va with mp 335°C. The salt dissolved when it was treated with ammonium hydroxide, and crystals precipitated from the solution when it was allowed to stand. The crystals were separated and dried to give a product with mp 250°C. No melting-point depression was observed for a mixture of this product with a sample of IVa.

Compounds IVb-e (Table 1) were similarly obtained.

B) A 0.8 g (5 mmole) sample of 2-amino-4-quinazolone and 0.54 g (5 mmole) of 3-chloropropionic acid were added successively to a solution of sodium ethoxide prepared from 0.11 g (4.7 g-atom) of sodium and 10 ml of absolute alochol, and the mixture was heated on a water bath for 2 h. It was then cooled, and the precipitated crystals were separated and crystallized from alcohol to give 0.7 g (63.6%) of 1,2,3,4-tetrahydropyrimido[2,1-b]quinazoline-2,6-dione (IVa) with mp 250°C. No melting-point depression was observed for a mixture of this product with a sample of the compound obtained by method A.

1-(β-Carboxypropyl)-1,2,3,4-tetrahydropyrimido[2,1-b]quinazoline-2,6-dione (VI). This compound was obtained by a method similar to that described above from 0.7 g (4.3 mmole) of amine I and 0.6 g (8.3 mmole) of acrylic acid. The yield was 0.9 g. IR spectrum: 1660, 1710, 1730 (C=O); 3150 cm^{-1} (OH).

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HETEROCYCLIC ANALOGS OF PLEIADIENE

XXXII.* SPIROPYRANS OF THE PERIMIDINE SERIES †

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Colorless spiropyrans were obtained by the reaction of 1,2,3-trimethyl and 1,3-dimethyl-2-ethylperimidinium iodides with salicylaldehyde and 2-hydroxy-1-naphthaldehyde in the presence of piperidine. When 5-nitrosalicylaldehyde is used, the reaction stops with the formation of a bright-orange merocyanine. The spiropyrans obtained have weakly expressed thermochromism; the spiropyrans obtained from 2-hydroxy-1-naphthaldehyde also have photochromic properties.

The formation of spiropyrans by the action of alkaline agents on o-hydroxystyryl derivatives of heterocyclic cations proceeds in two steps: the formation of a deeply colored merocyanine and its conversion to a usually colorless spiropyran as a result of intramolecular attack by the phenoxide oxygen atom on the carbon atom of the heterocyclic cation to which the styryl group is attached. The ease with which the second step occurs depends to a great degree on the effective positive charge on this carbon atom [3]. It has previously been shown that the perimidine molecule and especially its cation have one of the highest (in the diazole series) positive charges on the μ-carbon atom and a localization energy that is extremely favorable for spirocyclization [4, 5]. It therefore might have been expected that, in contrast to, for example, 2-(o-hydroxystyryl)benzimidazolium salts [6], the corresponding perimidinium salts would readily undergo conversion to spiropyrans.

Spiroyrans of the perimidine series were heretofore unknown. In the present research to synthesize them we used the condensation of perimidinium iodides (I, II) with salicylaldehyde, 5-nitrosalicylaldehyde, and 2-hydroxy-1-naphthaldehyde. Bright-red 1-methyl-2-(o-hydroxystyryl)perimidinium methiodide (III) is formed in 68% yield after a few minutes when salt I is heated with salicylaldehyde in alcohol in the presence of a catalytic amount of piperidine. It is very slightly soluble in water and organic solvents and therefore evidently does not lose a molecule of HI when it is treated with an aqueous solution of sodium carbonate or ammonium hydroxide. However, salt III gradually dissolves when it is refluxed in dimethylformamide (DMF) and is converted to colorless spiropyran IV. Spiropyran IV can be obtained immediately in 55% yield if the reaction of iodide I with salicylaldehyde is carried out in alcohol in the presence of excess piperidine. Spiropyran VI is formed very readily under the same conditions in the reaction of I with 2-hydroxy-1-naphthaldehyde. On the other hand, salt II does not react with aldehydes in alcohol solution, evidently because of the inductive and steric effects of the additional CH_3 group, which reduces the lability of the methylene hydrogen atoms. We were able to obtain spiropyrans V and VII only by refluxing salt II with the corresponding aldehydes in pyridine for many hours. (See Scheme on following page).

The structures of the spiropyrans are confirmed by the results of elementary analysis, the PMR and IR spectra, their lack of color, and their high solubility in organic solvents. Thus, for example, the PMR spectrum of spiropyran IV contains a quartet of signals at 6.3 ppm with an intensity of two proton units; this signal is

*See [1] for communication XXXI.

†Communication VIII from the series "Photochromic and Thermochromic Spirans." See [2] for communication VII.

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