SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF CERTAIN 3-(p-ALKOXYPHENYL)-6-HYDROXY- AND S-ALKYL-3-(p-BUTOXYPHENYL)-2-MERCAPTOQUINAZOL-4-ONES

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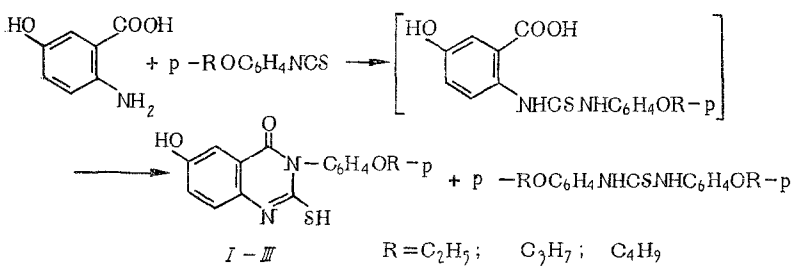
The present work is a continuation of the studies we started in [1]. 3-(p-Alkoxyphenyl)-5-hydroxy- (I-III, 9.v. Table 1), 3-(p-butoxyphenyl)-2-mercantoquinazol-4-one (IV), and the S-alkyl substituted compounds of IV (V-X) were prepared for the purpose of testing their tuberculostatic activity.

Compounds I-III were prepared from 5-hydroxyanthranilic acid [2] and p-ethoxy(propoxy-, butoxy-) phenylisothiocyanate. It was found on carrying out this reaction in boiling alcohol that it proceeded ambiguously—besides the 3-(p-alkoxyphenyl)-6-hydroxy-2-mercaptoquinazol-4-ones (I-III), 4,4'-dialkoxythiocarbanilides were isolated [3, 4]. The preparation of the thiocarbanilides can be explained by the formation of N-(p-hydroxy-o-carboxyphenyl)-N'-(p-alkoxyphenyl)thiourea in the first stage which on heating in alcohol by splitting off a molecule of water is converted into the corresponding quinazol-4-one (I-III) and besides this undergoes the symmetrization process previously known for N,N'-disubstituted thioureas [5] to form the energetically more favored 4,4'-dialkoxythiocarbanilides.



I-III R = C_2H_5; C_3H_7; C_4H_9

The two-stage process of formation of quinazol-4-ones was observed earlier during the condensation of anthranilic acid with phenylisothiocyanate in the cold—the intermediate N-phenyl-N'-(o-carboxyphenyl) thiourea was isolated [6].

The reaction of anthranilic acid with phenylisothiocyanate in boiling alcohol does not stop at the stage of formation of the intermediate thioureas but proceeds with the formation of 3-phenyl substituted 2-mercaptoquinazol-4-ones [7].

The original 5-hydroxyanthranilic acid was prepared from m-hydroxybenzoic acid through 6-nitro-3-hydroxybenzoic acid [8]. The latter was reduced with tin and hydrochloric acid analogously to the reduction of 4-nitro-m-hydroxybenzoic acid [2]. The catalytic reduction of 6-nitro-3-hydroxybenzoic acid in the presence of Raney nickel gave 5-hydroxyanthranilic acid which rapidly darkened in air.

All the obtained compounds were tested for tuberculostatic activity in the VNIKhFI chemeotherapy laboratory. The study was conducted by the serial dilution method in soytone medium without serum and with the addition of 10% horse serum. It was shown that the compounds with a hydroxy group in the 6-position of the quinazolone ring had little activity. 2-Mercapto-3-(p-propoxyphenyl)-6-hydroxy-quinazol-4-one (II, 32 μg/ml) stands out somewhat.

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TABLE 1. Chemical Constants and Tuberculostatic Activity of Compounds

Compound	R	R'	R''	Duration of reaction (in h)	Yield (in %)	Melting point (in deg.) from alcohol	Found (in %) C	H	N	S	Empirical formula	Calculated (in %) C	H	N	S	Tuberculostatic activity (in μg/ml)
I	H	C_2H_5	OH	7½	40	299—301	61,33	4,24	8,36	9,97	$C_{16}H_{14}N_2O_3S$	61,13	4,49	8,91	10,2	64
II	H	C_3H_7	OH	11½	34	314—16 (decomp.)	61,88	4,93	8,76	9,55	$C_{17}H_{16}N_2O_3S$	62,18	4,91	8,53	9,76	32
III	H	C_4H_9	OH	12½	94	305—7[1]	63,14	5,44	8,20	8,69	$C_{18}H_{18}N_2O_3S$	63,14	5,30	8,18	9,36	250
IV	H	C_4H_9	H	6	61	304—315[1]	66,57	5,58	8,33	9,76	$C_{18}H_{18}N_2O_2S$	66,24	5,56	8,58	9,85	500
V	C_4H_9	C_4H_9	H		89,6	123—5	69,33	7,01	7,35	8,14	$C_{22}H_{26}N_2O_2S$	69,08	6,85	7,32	8,38	64
VI	C_5H_{11}	C_4H_9	H		99	99—100	70,35	7,50	7,07	7,85	$C_{23}H_{28}N_2O_2S$	69,66	7,12	7,06	8,09	64
VII	iso-C_5H_{11}	C_4H_9	H		86,2	124—6	69,23	6,93	7,25	7,89	$C_{23}H_{28}N_2O_2S$					8
VIII	C_6H_{13}	C_4H_9	H		84,5	97—9	69,81	7,13	7,24	7,90	$C_{24}H_{30}N_2O_2S$	70,21	7,36	6,82	7,83	32
IX	C_7H_{15}	C_4H_9	H		66	80—81	70,84	7,44	6,76	7,50	$C_{25}H_{32}N_2O_2S$	70,72	7,60	6,60	7,55	16
X	$CH_2=CH-CH_2$	C_4H_9	H		90,6	126—8	68,42	5,97	7,89	8,52	$C_{21}H_{22}N_2O_2S$	68,84	6,05	7,64	8,75	125

[1]Substance crystallized from aqueous dimethylformamide.

The S-alkylation of 2-mercapto-3-(p-butoxyphenyl) quinazol-4-one (IV), which possessed very weak activity (500 μg/ml) with alkyl halides, led to an increase of activity up to 16 μg/ml (IX). 2-Isoamylmercapto-3-(p-butoxyphenyl) quinazol-4-one (VIII) shows the most activity (8 μg/ml). The tuberculostatic activity of the substances is reduced by the addition of serum.

EXPERIMENTAL

6-Nitro-3-hydroxybenzoic Acid was prepared by the nitration of m-hydroxybenzoic acid according to Beyer [8] and subsequent separation of the mixture of nitro products.

5-Hydroxyanthranilic Acid. To a hot solution of 16.5 g (0.0905 mole) of 6-nitro-3-hydroxybenzoic acid in 330 ml of concentrated hydrochloric acid was added gradually with stirring 50 g (0.421 mole) of tin. The reaction mixture was heated on a water-bath. After a day the precipitate was filtered off and the filtrate evaporated to dryness. The precipitate and the dry residue was dissolved in 400-450 ml of warm water and hydrogen sulfide was passed through the solution. The filtrate was evaporated until a solid began to separate. On cooling 13.86 g of acid hydrochloride was collected. The precipitate was dissolved in 200 ml of water. The solution was neutralized with a saturated solution of sodium acetate. The colorless precipitate was filtered off and washed well with water. The yield was 11.09 g (86.5%) of acid with mp 230°C (decomp.). According to the literature the mp is 233-234° [2], 218-248°—varies dependent on the heating, and 237-238° [10].

3-(p-Ethoxyphenyl)-6-hydroxy-2-mercaptoquinazol-4-one (I). A solution of 3.58 g (0.02 mole) of p-ethoxyphenylisothiocyanate in 50 ml of absolute alcohol was added with stirring to a boiling suspension of 1.53 g (0.01 mole) of 5-hydroxyanthranilic acid in 100 ml of absolute alcohol. The mixture was boiled and the solution evaporated to dryness. The residue was ground with ether, the precipitate was filtered off, and washed with ether. The yield was 1.77 g of a mixture of substances which was treated with 10% sodium hydroxide solution. 4,4'-Diethoxythiocarbanilide (0.26 g) with mp 170-171° (from alcohol, according to the literature data [3], the mp is 170-171°) was filtered off. From the alkaline filtrate 1.24 g of I (q.v. Table 1) was isolated with hydrochloric acid. By the analogous condensation of 5-hydroxyanthranilic acid with p-propoxy- or butoxyphenylisothiocyanate the corresponding 3-(p-propoxy- or butoxyphenyl)-6-hydroxy-2-mercaptoquinazol-4-one (II, III) was obtained. The reactions also proceeded ambiguously. 4,4'-Dipropoxythiocarbanilide with mp 182-184° (according to the literature [4] the mp is 184-186°) or 4,4'-dibutoxythiocarbanilide with mp 165-166° (according to the literature [3] the mp is 166-167°) was isolated as by-product. The melting

point of mixtures of isolated thiocarbanilide and thiocarbanilide obtained by the hydrogen sulfide method did not depress.

The constants, yield, analysis results, and tuberculostatic activity assays of all the obtained compounds are given in Table 1.

3-(p-Butoxyphenyl)-2-mercaptoquinazol-4-one (IV). A solution of 12.95 g (0.0628 mole) of p-butoxyphenylisothiocyanate in 20 ml of alcohol was added to a boiling solution of 8.56 g (0.0624 mole) of anthranilic acid in 60 ml of absolute alcohol. The mixture was boiled. After cooling, the colorless precipitate which separated was filtered off and crystallized from aqueous dimethylformamide (q.v. Table 1).

2-Isoamylmercapto-3-(p-butoxyphenyl)quinazol-4-one (VII). To a solution of 0.65 g (0.002 mole) of IV and 0.27 g of sodium hydroxide in 20 ml of 50% alcohol was added 0.5 g (0.0036 mole) of isoamyl bromide and the mixture was left for 2 days. After cooling the precipitate was filtered off and washed with water. V, VI, and VIII-X were prepared similarly. Substances V, VI, and VIII dissolved in organic solvents more readily than VII. Consequently, their isolation differed somewhat from the isolation of VII. The reaction mixture was evaporated, the residue was ground with water and filtered off.

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