SYNTHESIS OF SUBSTITUTED 2-PHENYL-6-HYDROXYQUINAZOLINES

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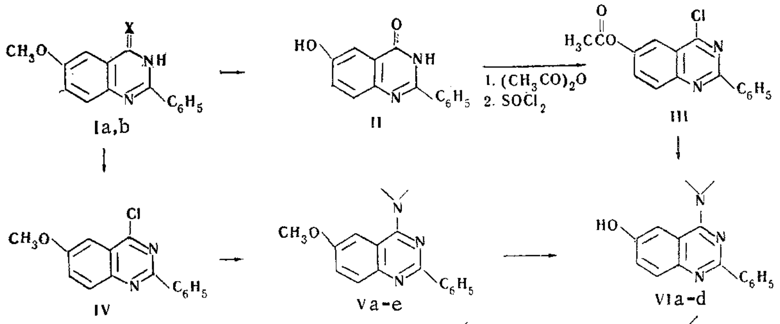
A method was developed for the synthesis of 2-phenyl-6-hydroxy(methoxy)quinazoline and a number of N-substituted 2-phenyl-4-amino-6-hydroxyquinazolines.

To obtain substituted quinazolinequinones by oxidative amination [1], we prepared a number of 2-phenyl-6-hydroxyquinazolines which contain amino groups (of various degrees of substitution) or hydrogen attached to C_4. These compounds are of independent interest since compounds with many-sided physiological activity have been observed among quinazolines in the last few years. Hydroxyquinazolines, in contrast to other phenyl-substituted quinazolines, have received inadequate study in this respect because of their lower accessibility. The syntheses of phenyl-substituted hydroxyquinazolines described in the literature are extremely complex [2, 3].

We have obtained a number of substituted 2-phenyl-6-hydroxyquinazolines from 2-phenyl-6-methoxy-4-quinazolone (Ia). The latter was recently synthesized from 1-(4-methoxyphenyl-2-phenylimidazoline-4,5-dione [4]. A more convenient, one-step method for the preparation of Ia involved the condensation of benzoyl-p-anisidine with ethylurethane (see [5]). Demethylation of Ia by heating with 75% sulfuric acid leads to II. This compound also forms by refluxing 2-phenyl-6-methoxyquinazoline-4-thione (Ib) [6] with 48% hydrobromic acid. After protection of the phenolic hydroxyl group in II by acetylation the acetate was converted to III by the action of thionyl chloride in the presence of dimethylformamide [7]. Chloride III gives high yields of N-substituted 2-phenyl-4-amino-6-hydroxyquinazolines (VIa-d) by heating with primary and secondary amines and alcohol, since aminolysis occurs simultaneously with halogen substitution.

A check of another path for the synthesis of VI (Ia → IV → V → VI) indicated that it is less acceptable, although shorter by one step. Compound V cannot be demethylated by heating with strong mineral acids in view of the instability of the quinazolines in acidic media [8]. Higher yields than in the first method were



Ia X = O, b X = S; V, VI a $-N\langle = -N(CH_2)_5$, b $-N\langle = -N(CH_2CH_2)_2O$, c $-N\langle = -C_4H_9NH$,
d $-N\langle = -NHC_6H_5$; Ve $-N\langle = -NHNHTs$

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TABLE 1. N-Substituted 2-Phenyl-4-amino-6-hydroxy(methoxy)-quinazolines

Compound	Mp, °C (crystallization solvent)	Empirical formula	Found, %			Calculated, %			Prep. method	Yield, %
			C	H	N	C	H	N		
Va	125—126, (alcohol)	$C_{20}H_{21}N_3O$	75,03	6,17	13,24	75,21	6,63	13,16		93
Vb	116—118, (alcohol)	$C_{19}H_{19}N_3O_2$	71,40	5,86	13,02	71,01	5,96	13,08		99
Vc	139—140, (heptane)	$C_{19}H_{21}N_3O$	74,37	6,87	13,70	74,24	6,89	13,67		88
Vd	155—156, (benzene)	$C_{21}H_{17}N_3O$	77,40	5,56	12,69	77,04	5,24	12,84		86
VIa	252—253, (alcohol)	$C_{19}H_{19}N_3O$	74,56	6,21	13,82	74,73	6,26	13,78	A B	84 63
VIb	278—279, (dioxane)	$C_{18}H_{17}N_3O_2$	70,20	5,80	13,60	70,34	5,57	13,67	A B	98 30
VIc	212—213, (ethyl acetate—heptane)	$C_{18}H_{19}N_3O$	73,71	6,56	14,50	73,65	6,57	14,32	A B*	98 10
VId	245—247, (chloroform—heptane)	$C_{20}H_{15}N_3O$	76,75	4,76	13,15	76,66	4,82	13,41	A B	95 36

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*A compound with mp 248-250° (from alcohol) was obtained via method B: 2-phenyl-4-butylamino-6-hydroxychloroquinazoline (the position of chlorine was not established). Found %: Cl 10.86; N 10.95. $C_{18}H_{18}ClN_3O$. Calculated %: Cl 10.95.

obtained by demethylation of V by means of aluminum chloride or pyridine hydrochloride (see [2, 9]). In addition, the demethylation of Vc with aluminum chloride leads to a reaction product which contains chlorine. The position occupied by the chlorine was not established, but halogenation apparently occurs at the 5-position of the quinazoline ring.

Alkaline cleavage of 4-hydrazinoquinazoline tosylates [9] was used to obtain 2-phenyl-6-hydroxy-(methoxy)quinazolines.

EXPERIMENTAL

2-Phenyl-6-methoxy-4-quinazolone (Ia). This was obtained by the method described in [5] by condensation of N-benzoyl-p-anisidine with ethylurethane in the presence of phosphoric anhydride in toluene. The product was obtained in 62% yield and had mp 260-261° (from dioxane) (mp 245° (decomp.) [4]). Found %: C 71.78; H 4.91; N 10.86. $C_{15}H_{12}N_2O_2$. Calculated %: C 71.41; H 4.80; N 11.11.

2-Phenyl-6-hydroxy-4-quinazolone (II). A. This compound was obtained in 97% yield by demethylation of Ia with 75% sulfuric acid according to the method in [1] and had mp 301-302° (from alcohol). Found %: C 70.44; H 4.50; N 11.38. $C_{14}H_{10}N_2O_2$. Calculated %: C 70.58; H 4.23; N 11.76.

B. The compound was also obtained in 59% yield by refluxing Ib in 48% hydrobromic acid for 6 h.

2-Phenyl-6-acetoxy-4-quinazolone. Acetylation of II in acetic anhydride–pyridine (3 : 2, by volume) gave 3.3 g (97%) of a product with mp 264-265° (from dioxane). Found %: C 68.41; H 4.23; N 10.00. $C_{16}H_{12}N_2O_3$. Calculated %: C 68.56; H 4.32; N 10.00.

2-Phenyl-4-chloro-6-acetoxyquinazoline (III). A mixture of 2.8 g (10 mmole) of 2-phenyl-6-acetoxy-4-quinazolone, 3 ml of dimethylformamide, and 20 ml of thionyl chloride was refluxed for 30 min, and the excess thionyl chloride was removed by vacuum distillation. The solid residue was dissolved in 60 ml of chloroform, and the resulting solution was washed successively with ice water (twice with 50-ml portions), 5% aqueous sodium bicarbonate (twice with 20-ml portions), and again with water (twice with 20-ml portions), dried with calcined potassium carbonate, and vacuum evaporated to give 2.5 g (83.5%) of colorless crystals with mp 128-130° (from heptane). Found %: Cl 12.10; N 9.43. $C_{16}H_{11}ClN_2O_2$. Calculated %: Cl 11.87; N 9.41.

2-Phenyl-4-chloro-6-methoxyquinazoline (IV). A mixture of 2.0 g (8 mmole) of Ia, 3.0 g (14 mmole) of phosphorus pentachloride, and 12 ml of phosphorus oxychloride was refluxed for 45 min, and the oxychloride was removed in vacuo. The residue was dissolved in chloroform, and the solution was washed with water with 5% aqueous sodium bicarbonate, dried with sodium sulfate, and the chloroform was removed by distillation to give 1.7 g (79%) of colorless crystals which were quite soluble in chloroform and benzene and had mp 131-132° (from hexane). Found %: Cl 12.94; N 10.13. $C_{15}H_{11}ClN_2O$. Calculated %: Cl 13.10; N 10.35.

N-Substituted 2-Phenyl-4-amino-6-methoxyquinazolines (Va-d). Compound IV [2.7 g (10 mmole)] was added to a solution of 25 mmole of amine (piperidine, morpholine, butylamine, or aniline) in 10 ml of absolute ethanol, and the mixture was refluxed for 2 h. Compounds Va and Vc were isolated by diluting the reaction mass with water and triturating the liberated oily residue with 1% sodium hydroxide; Vb was precipitated as the base, while Vd was precipitated as the hydrochloride (mp 264-265°, from alcohol), which was converted to the base by the action of ammonia in alcohol.

The constants and yields of the synthesized compounds are presented in Table 1.

N-Substituted 2-Phenyl-4-amino-6-hydroxyquinazolines (VI). A. Compound III [1.45 g (5 mmole)] was added to a solution of 30 mmole of amine (piperidine, morpholine, butylamine, or aniline) in 10 ml of absolute alcohol, and the mixture was refluxed for 2 h. Products VIa and VIb precipitated on cooling; VIc was isolated by diluting the reaction mass with water, neutralizing the excess amine with acetic acid, and triturating the oily residue with water until it began to crystallize. Compound VId precipitated from the reaction mass as the hydrochloride, which was dissolved in the cold in 4% sodium hydroxide, treated with charcoal, and neutralized with acetic acid (Table 1).

B. A mixture of 5 mmole of V and 1.33 g (10 mmole) of anhydrous aluminum chloride in 30 ml of xylene was refluxed with stirring for 5 h. The reaction mass was cooled, the xylene was decanted, and the residue was washed with ether and treated with 10 ml of ice water to which 1 ml of 10% hydrochloric acid had been added. The precipitate was separated, dissolved in 4% sodium hydroxide, treated with charcoal, and neutralized with acetic acid. The resulting precipitate was filtered, washed with water, dried, and recrystallized (Table 1).

2-Phenyl-4-hydrazino-6-methoxyquinazoline p-Toluenesulfonate Hydrochloride (Ve). A solution of 3.7 g (20 mmole) of p-toluenesulfonic acid hydrazide in 30 ml of chloroform was added to a solution of 5.4 g (20 mmole) of IV in 30 ml of warm chloroform, and the mixture was allowed to stand for 3 days at room temperature. The resulting white precipitate was filtered and dried to give 8.5 g (93%) of a product with mp 228-229° (decomp.). The compound was used without purification for the next step.

2-Phenyl-6-methoxyquinazoline. Compound Ve [8.2 g (18 mmole)] was added in portions in the course of 20 min with stirring to a solution of 1.6 g (40 mmole) of sodium hydroxide and 0.5 g (5 mmole) of sodium carbonate in 160 ml of water at 95-100°. The mixture was heated for 2 h on a water bath (nitrogen evolution was observed during this process), cooled, and the resulting precipitate was filtered, washed with water, and dried, and the reaction product was extracted with boiling heptane. Evaporation of the extract to a small volume yielded 1.9 g (45%) of light-yellow crystals of 2-phenyl-6-methoxyquinazoline with mp 116-117° (from heptane). Found %: C 76.30; H 5.17; N 11.78. $C_{15}H_{12}N_2O$. Calculated %: C 76.25; H 5.12; N 11.86.

2-Phenyl-4-hydrazino-6-acetoxyquinazoline p-Toluenesulfonate Hydrochloride. This was obtained in the same way as Ve in 96% yield and had mp 222-224° (decomp.). The compound was used without purification for the next step.

2-Phenyl-6-hydroxyquinazoline. 2-Phenyl-4-hydrazino-6-acetoxyquinazoline p-toluenesulfonate hydrochloride [4.8 g (10 mmole)] was added in portions with stirring in the course of 30 min to a solution of 2 g (50 mmole) of sodium hydroxide and 1 g (10 mmole) of sodium carbonate in 100 ml of water at 95-100°. The mixture was heated for 1 h at 95-100°, treated with charcoal, neutralized at 80° with acetic acid, and cooled. The resulting precipitate was filtered, washed with water, and dried to give 1.9 g (85%) of light-yellow crystals with mp 235-236° [from acetone–water (1 : 1)]. Found %: C 75.94; H 4.50; N 12.52. $C_{14}H_{10}N_2O$. Calculated %: C 75.66; H 4.53; N 12.61.

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