RESEARCH IN THE CHEMISTRY OF PHENOXAZINES

IX.* PREPARATION OF AMINO DERIVATIVES OF 7-HYDROXY-3-PHENOXAZINONE

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UDC 547.867.6.7

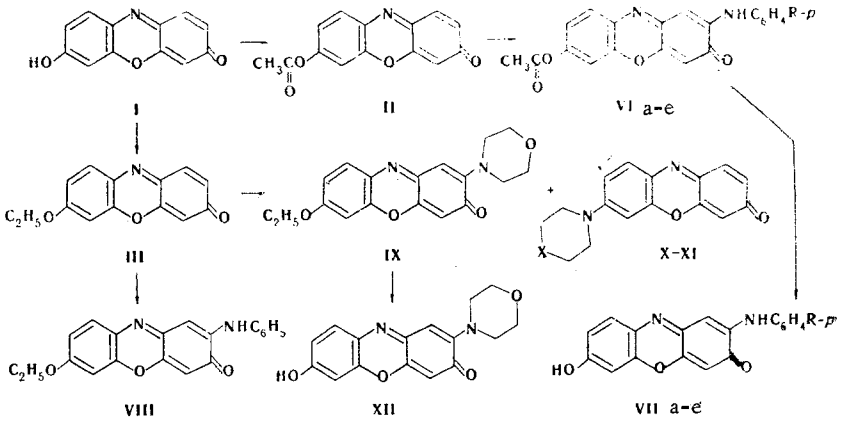
Reaction of 7-acetoxy- or 7-ethoxy-3-phenoxazinone with amines gave 2- and 7-amino derivatives of 3-phenoxazinone.

Amino derivatives of phenoxazines have diverse kinds of physiological activity [2, 3]. Because of the absence of a practicable method of preparation in this direction, amino derivatives of 3-phenoxazinone have not been studied.

It has been shown that 7-hydroxy-3-phenoxazinone (resorufin) (I) undergoes a smooth nucleophilic substitution reaction with thiophenols to give 2,8-di(arylthio)derivatives [4]. A similar reaction of I with amines might have been expected. However, by virtue of its appreciable acidity (pK_a 6.85), resorufin reacts with amines to give only salts, which are readily decomposed during recrystallization. In the case of a stronger acid – 2,4,6,8-tetrabromoresorufin (IV) [5] (pK_a 2.16) – salts can be isolated in pure form. Thus, IV reacts with morpholine to give bright-green salt V, the electronic spectrum of an alcohol solution of which contains the maximum of the anion of 2,4,6,8-tetrabromoresorufin (λ_{max} 608 nm).

Amino derivatives of resorufin were obtained from 7-acetoxy- (II) [5] and 7-ethoxy-3-phenoxazinone (III) [6] with subsequent removal of the protective group.

Compound II reacts readily with aromatic amines (pK_a 1-5) on refluxing in alcohol solution in the presence of the amine hydrochlorides to give 2-monosubstituted derivatives IVa-e. Entry of the amines into the 2-position was previously confirmed in the case of the reaction [1] of 3-phenoxazinone with ammonia.

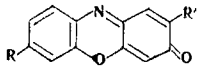


VI, VII a R = H, b R = Br, c R = OCH_3, d R = CH_3, e R = NO_2; X X = O; XI X = CH_2

* See [1] for communication VIII.

S. M. Kirov Polytechnic Institute, Severdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1196-1199, September, 1974. Original article submitted November 5, 1973.

TABLE 1



Compound	R	R′	mp, °C	Empirical formula	Found, %			Calc., %			λ_{max}, nm (lg ε)	Yield, %
					C	H	N	C	H	N		
VIa	$OCOCH_3$	NHC_6H_5	246—248[a]	$C_{20}H_{14}N_2O_4$	69,5	4,3	7,9	69,4	4,1	8,1	446 (4,38)	60
VIb	$OCOCH_3$	NHC_6H_4Br	263—265[b]	$C_{20}H_{13}BrN_2O_4$	56,7	3,0	—	56,9	3,1	—	450 (4,08) 580 (3,91)	70
VIc	$OCOCH_3$	$NHC_6H_4OCH_3$	214—216[b]	$C_{21}H_{16}N_2O_5$	67,2	4,3	7,1	67,2	4,3	7,5	442 (4,39) 580 (4,37)	65
VId	$OCOCH_3$	$NHC_6H_4CH_3$	200—202[a]	$C_{21}H_{16}N_2O_4$	69,9	4,3	7,7	70,2	4,5	7,8	440 (4,34) 578 (4,13)	60
VIe	$OCOCH_3$	$NHC_6H_4NO_2$	>350[c]	$C_{20}H_{13}N_3O_6$	61,3	3,5	10,5	61,5	3,4	10,8	462 —	80
VIIa	OH	NHC_6H_5	>300[b]	$C_{18}H_{12}N_2O_3$[e]	71,2	4,2	9,0	71,2	4,0	9,3	472 (4,46) 574 (4,02)	80
VIIb	OH	NHC_6H_4Br	>300[c]	$C_{18}H_{11}BrN_2O_3$[f]	56,7	3,0	—	56,4	2,9	—	472 (4,31)	85
VIIc	OH	$NHC_6H_4OCH_3$	264—266[a]	$C_{19}H_{14}N_2O_4$[g]	68,2	4,1	8,5	68,3	4,2	8,4	466 (4,39) 578 (4,24)	80
VIId	OH	$NHC_6H_4CH_3$	282—284[a]	$C_{19}H_{14}N_2O_3$[h]	71,6	4,6	9,0	71,8	4,4	8,9	468 (4,42)	80
VIIe	OH	$NHC_6H_4NO_2$	>350[c]	$C_{18}H_{11}N_3O_5$	62,1	3,3	12,6	62,0	3,2	12,1	466 —	85
VIII	OC_2H_5	NHC_6H_5	207—209[b]	$C_{20}H_{16}N_2O_3$[i]	72,5	5,1	—	72,4	4,9	—	468 (4,52)	60
IX	OC_2H_5	$N(CH_2CH_2)O$	223—225[b]	$C_{18}H_{19}N_2O_4$[j]	66,7	5,7	9,0	66,4	5,6	8,6	460 (4,4)	30
X	$N(CH_2CH_2)O$	H	>300[b]	$C_{16}H_{14}N_2O_3$[k]	68,2	5,3	10,4	68,2	5,0	10,0	556 (4,65)	40
XI	$N(CH_2CH_2)CH_2$	H	246—248[d]	$C_{17}H_{16}N_2O_3$[l]	72,7	5,8	10,6	73,0	5,8	10,0	580 (5,0)	30
XII	OH	$N(CH_2CH_2)O$	260—262[d]	$C_{16}H_{14}N_2O_4$	—	—	9,2	—	—	9,4	472 (4,75)	22

[a]From isoamyl alcohol. [b]From butanol. [c]From dimethylformamide. [d]From ethanol. [e]pK_a 7.62 ± 0.03. [f]Found, %: Br 20.8. Calculated, %: Br 20.8. pK_a 7.58 ± 0.02. [g]pK_a 7.74 ± 0.02. [h]pK_a 7.95 ± 0.01. [i]R_f 0.718. [j]R_f 0.354. [k]R_f 0.182. [l]R_f 0.218.

The resulting 2-amino-3-phenoxazinone was also obtained by an independent method from 0-aminophenol [7]. Saponification of the acetoxy group in VIa-e with sodium ethoxide gives 2-arylaminoresorufins VIIa-e, which are dark-gray crystalline substances that dissolve in alkali to give violet solutions. The pK_a values of VIIa-d are higher than the pK_a value of resorufin (Table 1), i.e., the introduction of arylamino groups into the 2-position of the resorufin molecule hinders acid–base ionization of the hydroxyl group.

Transacylation leading to resorufin and the corresponding acetylamine occurs in the reaction of II with stronger amines (pK_a 8-11). Thus, pure resorufin was isolated in the reaction of II with morpholine.

Like 3-phenoxazinone, III reacts with aromatic amines to give 2-substituted derivatives (for example, VIII). The reaction of III with morpholine and piperidine proceeds peculiarly. In the case of morpholine, a mixture of two products (IX-X), which differ in color and R_f values (Table 1), is formed. In addition to entry of morpholine into the quinoid ring (IX), the ethoxy group undergoes nucleophilic substitution by morpholine to give X (the electrophilicity of the 7-position of the phenoxazinone molecule was previously confirmed by calculations by the Hückel MO method [8]). The latter reaction becomes the dominant one in the reaction of III with a stronger amine – piperidine. 7-Piperidino-3-phenoxazinone (XI) is the primary product in this case. The isomer with an amino group in the 2-position could not be isolated, although its presence in very small amounts can be assumed from thin-layer chromatography (TLC) of the reaction mixture.

In contrast to the acetoxy group, the ethoxy group is saponified in acidic media. Thus, 2-morpholinoresorufin (XII) was obtained by heating IX in 75% H_2SO_4.

EXPERIMENTAL

The electronic spectra of alcohol solutions of the compounds were recorded with an SF-10 spectrophotometer. The ionization constants were measured spectrophotometrically with an SF-4 spectrophotometer by the method in [9].

2,4,6,8-Tetrabromoresorufin Morpholine Salt (V). A 1.5-ml sample of morpholine was added to 0.5 g (1 mmole) of 2,4,6,8-tetrabromoresorufin in 15 ml of alcohol, and the mixture was heated on a water bath for 3 h. The resulting green precipitate was removed by filtration, washed with alcohol, and crystallized from dimethylformamide (DMFA) to give 0.4 g (75%) of V. Found, %: C 31.8; H 2.1; N 4.7. $C_{16}H_{12}N_2O_4Br_4$. Calculated, %: C 31.3; H 1.8; N 4.6.

Compounds VIa-e. A 1-ml sample of the amine was added to 3.9 mmole and II and 0.77 mmole of the amine hydrochloride in 25 ml of alcohol, and the mixture was refluxed for 30 min. It was then cooled, and the crystals that precipitated from the brown solution were removed by filtration and washed with alcohol to give 0.6 g of product (Table 1).

Compounds VIIa-e. A 1.4-mmole sample of VI was added to a solution of sodium ethoxide (0.3 g of sodium in 30 ml of alcohol), and the mixture was refluxed on a water bath for 15 min. The precipitated sodium salt of VII was removed by filtration and treated with dilute hydrochloric acid. The precipitate was again removed by filtration and washed with water and alcohol to give 0.4 g of product (Table 1).

2-Phenylamino-7-ethoxy-3-phenoxazinone (VIII). Aniline (2 ml) was added to 0.35 g (1.5 mmole) of III in 10 ml of alcohol, and the mixture was refluxed for 10 h. The precipitate that formed on cooling was removed by filtration and washed with alcohol and ether to give 0.2 g of product (Table 1).

2-Morpholino-7-ethoxy-3-phenoxazinone (IX) and 7-Morpholino-3-phenoxazinone (X). Morpholine (4 ml) and 0.2 g (1.6 mmole) of morpholine hydrochloride were added to 1 g (4 mmole) of III in 25 ml of alcohol, after which the mixture was refluxed for 16 h. The mixture was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, dried, and chromatographed with benzene–ether (3 : 1) in a column filled with aluminum oxide (activity III). The first dark-yellow fraction was collected and evaporated to give 0.3 g of IX. The second violet fraction was collected and evaporated to give 0.3 g of X (Table 1). Each compound was subjected to crystallization.

7-Piperidino-3-phenoxazinone (XI). Piperidine (1.5 ml) and 0.2 g (1.6 mmole) of piperidine hydrochloride were added to 0.5 g (2 mmole) of III in 15 ml of alcohol, and the mixture was refluxed for 16 h. It was then cooled, and the solvent was evaporated. The resulting precipitate was removed by filtration, washed with alcohol, and dried. It was then chromatographed with a column filled with activity III aluminum oxide with elution by anhydrous chloroform to give a violet fraction. The solvent was evaporated, and the residue was crystallized to give 0.15 g of product (Table 1).

2-Morpholino-7-hydroxy-3-phenoxazinone (XII). A 0.5-g (1.6 mmole) sample of IX was dissolved in 10 ml of 75% sulfuric acid, and the solution was heated carefully on a water bath for 15 min. It was then cooled, treated with 20 ml of water, and neutralized to pH 3 with sodium carbonate. The resulting precipitate was removed by filtration and washed with water to give 0.1 g of product.

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