DIRECT AMINATION OF 3-PHENOTHIAZONE

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UDC 547.869:542.958.3

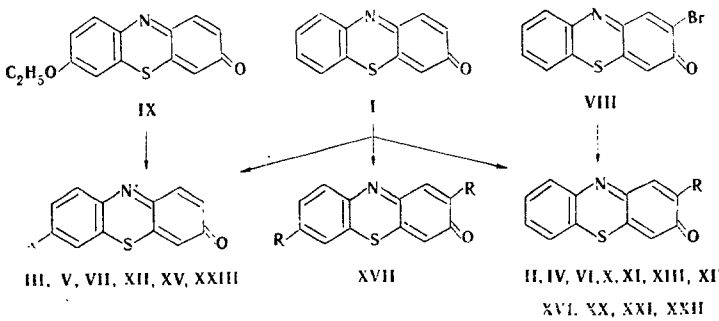
3-Phenothiazone reacts with primary and secondary aliphatic and aromatic amines to give 2- and 7-monoamino derivatives. Replacement of the bridge oxygen atom of 3-phenoxazinone by a sulfur atom leads to an increase in the reactivity of the 7 position and to a bathochromic shift of the long-wave absorption band in the electronic spectrum.

Ginzburg and Sevbo [1] recently synthesized 2-amino-3-phenothiazone, which has considerable physiological activity. Inasmuch as we have previously developed a convenient method for the preparation of amino derivatives of 3-phenoxazinone [2, 3], it seemed of interest to extend this reaction to the sulfur isoanalog of 3-phenoxazinone — 3-phenothiazone — in order to obtain new compounds for chemotherapeutic tests and to study the effect of the bridge atom (sulfur and oxygen, respectively, in phenoxazinone and phenothiazone) on the physicochemical properties and reactivities of the compounds. In the present research we studied the reaction of 3-phenothiazone with cycloalkylimines and aromatic and aliphatic amines and made a comparison of the products with the analogous 3-phenoxazinone derivatives. 3-Phenothiazinone reacts smoothly with cycloalkylimines on heating in benzene or alcohol. In contrast to the reaction with 3-phenoxazinone, in which only the 2-cycloalkylimino derivatives are formed, two products (see the scheme on p. 309). II-III, IV-V, and VI-VII) that differ with respect to their colors, melting points, and R_f values were isolated in the case of reactions with 3-phenothiazone. Elementary analysis showed that these compounds are isomeric monosubstituted 3-phenothiazones. In analogy with 3-phenoxazinone [2] it might be assumed that II, IV, and VI, which have lower melting points, R_f values of 0.54-0.84, and a hypsochromic shift of the first absorption band (relative to the starting 3-phenothiazone), contain a cycloalkylimine residue in the quinoid ring, whereas III, V, and VII, which have high melting points, R_f values of 0.12-0.43, and a bathochromic shift of the first absorption band, contain a cycloalkylimine residue in the benzoid ring. To prove this assumption we carried out reactions in which we used compounds with a known orientation of substituents. Thus a compound identical to the product of the reaction of 3-phenothiazone with morpholine (II) was obtained from the reaction of 2-bromo-3-phenothiazone (VIII) [4] with morpholine, whereas a product (IX) [5] identical to III (see the scheme on p. 309) was obtained from 7-ethoxy-3-phenothiazone.

3-Phenothiazone reacts readily with aliphatic amines. 2-Methylamino-3-phenothiazone (X) was obtained when methylamine was bubbled through a solution of 3-phenothiazone. 2-Diethylamino-3-phenothiazone (XI) and 7-diethylamino-3-phenothiazone (XII) were obtained by heating 3-phenothiazone with diethylamine in dimethylformamide (DMFA). In contrast to 3-phenoxazinone, which forms 2-amino-3-phenoxazinone when it is heated in alcohol with ammonia in sealed tubes, a product of this sort could not be obtained from 3-phenothiazone under these conditions.

Differences from 3-phenoxazinone are also observed in the reaction of 3-phenothiazone with aromatic amines. Thus monosubstitution products — 2-methylanilino-3-phenothiazone (XIV) and 7-methylanilino-3-phenothiazone (XV) — are formed in the reaction of 3-phenothiazone with methylaniline.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 353-357, March, 1975. Original article submitted May 14, 1974.



II, III R = morpholino IV, V R = piperidino VI, VII R = cyclohexylamino X R = $=NHCH_3$; XI, XII R = $N(C_2H_5)_2$; XIII R = $NHC_{16}H_{14}$; XIV, XV R = $NCH_3C_6H_5$; XVI, XVII R = NHC_6H_5; XX R = NH-*p*-$C_6H_4NO_2$; XXI R = NH-*p*-$C_6H_4OCH_3$; XXII, XXIII R = $NC_2H_5C_6H_5$.

The reaction with ethylaniline proceeds similarly to give XXII and XXIII. Only 2-anilino-3-phenoxazinone (XIX) is formed in the reaction of 3-phenoxazinone (XVIII) with aniline, whereas a small amount of a product whose elementary analysis indicates the presence of two aniline residues in the 3-phenothiazone molecule is obtained along with 2-anilino-3-phenothiazone (XVI) in the case of 3-phenothiazone. Upon observing the formation of 2- and 7-monosubstituted 3-phenothiazones we assumed that the product is 2,7-dianilino-3-phenothiazone (XVII). A partial confirmation of the structure of the product is its formation from 2-anilino-3-phenothiazone (XVI) on reaction with aniline. Only 2-anilino-3-phenothiazone was isolated when the reaction of 3-phenothiazone with aniline was carried out in acetic acid or DMFA under the conditions indicated in [6].

A comparison of the electronic absorption spectra (Table 1) shows that all of the 2-amino derivatives have a hypsochromic shift, whereas the 7-amino derivatives have a bathochromic shift of the long-wave band relative to the starting 3-phenothiazone. At the same time, 3-phenothiazone and all of its derivatives have deeper coloration (a bathochromic shift of 30-50 nm) than the corresponding compounds of the 3-phenoxazinone series [2]. This is probably associated with the greater possibility of saturation of the quinoid fragment of the 3-phenothiazone molecule during the $\pi_1 \rightarrow \pi^*_1$ transition due to the electrons of the sulfur atom as compared with the 3-phenoxazinone molecule, in which the $\pi_1 \rightarrow \pi^*_1$ transition, as shown in [7], is due to transfer of the electron density from the benzoid portion of the molecule to the quinoid portion.

Thus replacement of the bridge oxygen atom in 3-phenoxazinone by a sulfur atom leads to an increase in the reactivity of the 7 position and a bathochromic shift of the long-wave band in the electronic spectrum.

EXPERIMENTAL

The electronic spectra of chloroform solutions of the compounds ($5 \cdot 10^{-4}$ M) in the visible region were recorded with an SF-10 spectrophotometer. The R_f values were determined on Silufol UV-254 in a benzene–ether system (3:1). The compounds were separated on activity II Al_2O_3 in the following systems: benzene for I, benzene–acetone (3:1) for II-VII, XVI, XVII, and XXI, benzene–ether (5:1) for XI and XII, toluene–ether (4:1) for XIII, benzene–ether (2:1) for XIV, XV, XXII, and XXIII, and anhydrous chloroform for XIX and XX. 3-Phenothiazone was obtained by the method in [8]. 3-Phenoxazinone was obtained by the method in [9].

2-Morpholine-3-phenothiazone (II) and 7-Morpholino-3-phenothiazone (III). A) A 1.5-ml (18 mmole) sample of morpholine and a fourfold excess of morpholine hydrochloride or 0.5 ml of concentrated hydrochloric acid were added to 0.5 g (2.3 mmole) of I in 15 ml of ethanol, and the mixture was refluxed on a water bath for 6 h. The solvent was evaporated, and the residue was dissolved in benzene–acetone (3:1) and chromatographed. The first orange fraction was collected, and evaporation of the solvent and crystallization of the residue gave 0.3 g (60%) of II. Evaporation of the solvent from the second bright-crimson fraction and crystallization of the residue gave 0.1 g (20%) of III.

B) A 1.5-ml (18 mmole) sample of morpholine was added to 0.5 g (2.3 mmole) of I in 15 ml of benzene, and the mixture was refluxed on a water bath for 10 h. It was then chromatographed, and the solvent was removed from the fractions. The first fraction yielded 0.22 g (44%) of II, and the second fraction yielded 0.09 g (18%) of III.

TABLE 1. Amino-3-phenothiazones

Compound	mp, °C	Empirical formula	Found, %				Calc., %				R_f[a]	λ_{max}, nm	lg ε	Yield, %
			C	H	N	S	C	H	N	S				
II	199—200 b	$C_{16}H_{14}N_2O_2S$	64,6	4,7	9,0	11,0	64,5	4,7	9,4	10,7	0,52	471	4,35	43
III	238—239 b	$C_{16}H_{14}N_2O_2S$	64,5	4,6	9,0	10,9	64,5	4,7	9,4	10,7	0,12	542	5,26	14
IV	123—125 c	$C_{17}H_{16}N_2OS$	68,9	5,5	9,5	—	68,8	5,4	9,5	—	0,78	475	4,15	29
V	216—217 c	$C_{17}H_{16}N_2OS$	68,8	5,4	9,4	—	68,8	5,4	9,5	—	0,32	556	4,78	14
VI	111—112 c	$C_{18}H_{18}N_2OS$	70,1	5,8	8,8	9,9	69,8	5,8	9,0	10,3	0,84	454	3,82	28
VII	187—189 c	$C_{18}H_{18}N_2OS$	69,5	5,8	8,8	10,0	69,8	5,8	9,0	10,3	0,48	566	4,76	13
X	129—130 b	$C_{13}H_{10}N_2OS$	59,8	4,8	12,7	14,7	60,5	4,7	12,8	14,7	0,60	480	3,56	21
XI	111—112 b	$C_{16}H_{16}N_2OS$	67,6	5,6	9,5	11,3	67,6	5,6	9,8	11,3	0,75	482	4,20	49
XII	190—192 c	$C_{16}H_{16}N_2OS$	67,2	5,4	9,9	11,4	67,6	5,6	9,8	11,3	0,16	530	4,65	11
XIII	134—135 d	$C_{22}H_{21}N_2OS$	43,1	6,2	8,3	9,1	43,0	5,8	7,8	8,9	0,95	472	3,91	42
XVI	245—246 e	$C_{18}H_{12}N_2OS$	70,9	3,9	9,0	10,4	71,0	4,0	9,2	10,5	0,88	490	3,56	40
XVII	276—277 d	$C_{24}H_{17}N_3OS$	72,9	4,3	10,5	7,4	72,8	4,0	10,6	8,1	0,62	567	4,54	6
XIV	162—163 e	$C_{19}H_{14}N_2OS$	71,6	4,5	9,0	—	71,8	4,4	8,9	—	0,80	453	4,31	32
XV	209—210 f	$C_{19}H_{14}N_2OS$	71,7	4,9	9,0	—	71,8	4,4	8,9	—	0,15	485	3,98	10
XX	259—260d	$C_{18}H_{11}N_3O_3S$	61,9	3,3	12,2	9,3	61,9	3,2	12,0	9,2	0,77	490	4,25	47
XXI	198—199 f	$C_{19}H_{14}N_2O_2S$	68,3	4,2	8,7	9,6	68,2	4,2	8,4	9,6	0,82	477	4,23	45
XIX	214—216 b	$C_{18}H_{12}N_2O_2$	74,8	4,4	10,1	—	75,0	4,2	9,7	—	0,54	448	4,45	35
XXII	192—193 e	$C_{20}H_{16}N_2OS$	72,2	4,6	8,6	9,5	72,3	4,8	8,4	9,6	0,68	469	4,49	46
XXIII	245—246 b	$C_{20}H_{16}N_2OS$	—	—	8,5	9,6	—	—	8,4	9,6	0,29	561	4,60	12

a) The product was eluted with benzene—ether (1:1). b) From butyl alcohol and ethanol (1:3). c) From DMFA—water (4:3). d) From butyl alcohol. e) From acetic acid.

C) A 0.75-ml (9 mmole) sample of morpholine was added to 0.2 g (0.7 mmole) of 2-bromo-3-phenothiazone (VIII) in 10 ml of acetic acid, and the mixture was refluxed for 1 h. It was then poured into 100 ml of water, and the aqueous solution was extracted with benzene. The extract was washed with water and evaporated, and the residue was dissolved in benzene—acetone (3:1) and chromatographed. An orange fraction was collected, from which the solvent was evaporated, and the residue was crystallized to give 0.1 g of II, which, according to its melting point, R_f value, elementary analysis, and electronic spectrum in the visible region, is identical to the compound obtained from 3-phenothiazone by methods A and B.

D) A 1.5-ml (18 mmole) sample of morpholine was added to 0.5 g (1.9 mmole) of 7-ethoxy-3-phenothiazone (IX) in alcohol in the presence of 0.5 ml of concentrated hydrochloric acid, and the mixture was refluxed on a water bath of 8 h. The solvent was then evaporated, and the residue was dissolved in benzene—acetone (3:1) and chromatographed. An orange fraction was collected, from which the solvent was evaporated, and the residue was crystallized to give 0.25 g of III, which, with respect to its melting point, R_f value, elementary analysis, and electronic spectrum in the visible region, is identical to the compound obtained from 3-phenothiazone by methods A and B.

2-Piperidino-3-phenothiazone (IV) and 7-Piperidino-3-phenothiazone (V). The methods used to obtain II and III were used to obtain these compounds from 0.5 g (2.3 mmole) of I and 2 ml (20 mmole) of piperidine (method B). The yields of IV and V, respectively, were 0.2 g (40%) and 0.1 g (20%).

2-Cyclohexamethyleneimino-3-phenothiazone (VI) and 7-Cyclohexamethyleneimino-3-phenothiazone (VII). These compounds were similarly obtained by method B from 0.5 g (2.3 mmole) of I and 2 ml (20 mmole) of cyclohexamethyleneimine. The yields of VI and VII, respectively, were 0.22 g (44%) and 0.1 g (20%).

2-Methylamino-3-phenothiazone (X). Methylamine was bubbled through a solution of 0.5 g (2.3 mmole) of I in 20 ml of DMFA at room temperature for 1 h, after which the reaction mixture was poured into 150 ml of water, and the aqueous solution was extracted with chloroform. The extracts were washed with four 100-ml portions of water and dried over calcium chloride. The solution was concentrated to 10 ml and separated with a column filled with KSK silica gel with elution by anhydrous chloroform. The first red-brown fraction was collected and evaporated, and the residue was crystallized to give 0.17 g of X.

2-Diethylamino-3-phenothiazone (XI) and 7-Diethylamino-3-phenothiazone (XII). A 3-ml (18 mmole) sample of diethylamine and 1 g of diethylamine hydrochloride were added to 0.5 g (2.3 mmole) of I in 10 ml of DMFA, and the mixture was heated at 50° for 3.5 h. It was then

poured into 100 ml of water, and the resulting precipitate was removed by filtration, washed with water, dried, dissolved in benzene–ether (5:1), and chromatographed. The first reddish-brown fraction was collected, the solvent was evaporated, and the residue was crystallized to give 0.3 g (60%) of XI. Evaporation of the solvent from the second bright-blue zone and crystallization of the residue gave 0.15 g (30%) of XII.

2-Adamantylamino-3-phenothiazone (XIII). A 0.5-ml sample of concentrated hydrochloric acid and 0.8 g of aminoadamantane (12 mmole) were added to 0.5 g (2.3 mmole) of I in 15 ml of DMFA, and the mixture was heated on a water bath for 5 h. It was then poured into 150 ml of water, and the resulting precipitate was removed by filtration, washed with water, dried, dissolved in toluene–ether (4:1), and chromatographed. The orange fraction was collected, the solvent was evaporated, and the residue was crystallized to give 0.28 g (50%) of XIII.

2-Methylanilino-3-phenothiazone (XIV) and 7-Methylanilino-3-phenothiazone (XV). A 1.6-ml (17 mmole) sample of methylaniline and 0.68 g of methylaniline hydrochloride were added to 0.5 g (2.3 mmole) of I in 15 ml of ethanol, and the mixture was refluxed for 5 h. The solvent was evaporated, and the residue was dissolved in benzene–ether (2:1) and chromatographed. The first brown fraction was collected, the solvent was evaporated, and the residue was crystallized to give 0.2 g (40%) of XIV. Evaporation of the solvent from the violet zone and crystallization of the residue gave 0.1 g (20%) of XV.

2-Anilino-3-phenothiazone (XVI) and 2,7-Dianilino-3-phenothiazone (XVII). A 1.5-ml (16 mmole) sample of aniline and 0.8 g of aniline hydrochloride were added to 0.5 g (2.3 mmole) of I in 15 ml of ethanol, and the mixture was refluxed on a water bath for 3 h. The solvent was evaporated, and the residue was dissolved in benzene–acetone (3:1) and chromatographed. The first yellow-red zone was collected, the solvent was evaporated, and the residue was crystallized to give 0.3 g (60%) of XVI. Evaporation of the solvent from the lilac-colored zone and crystallization of the residue gave 0.08 g (16%) of XVII.

2-Anilino-3-phenoxazinone (XIX). A 1-ml (10 mmole) sample of aniline and 0.7 g of aniline hydrochloride were added to 0.4 g of 3-phenoxazinone (XVIII) in 15 ml of alcohol, and the mixture was refluxed on a water bath for 6 h. The solvent was then evaporated, and the residue was chromatographed. A reddish-orange fraction was collected, the solvent was evaporated, and the residue was crystallized to give 0.2 g (50%) of XIX.

2-(p-Nitroanilino)-3-phenothiazone (XX). A 1.3-g (10 mmole) sample of p-nitroaniline was added to 0.5 g (2.3 mmole) of I in 20 ml of acetic acid, and the mixture was refluxed for 3 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with water. The mother liquor was poured into 100 ml of water, and the aqueous mixture was extracted with benzene. The benzene extracts were washed with water, the solvent was evaporated, and the residue was added to the precipitate. The solid product was dissolved in chloroform and chromatographed. The first reddish-brown fraction was collected, the solvent was evaporated, and the residue was crystallized to give 0.38 g of XX.

2-(p-Anisidino)-3-phenothiazone (XXI). A 0.5-ml sample of concentrated hydrochloric acid was added to 0.5 g (2.3 mmole) of I in 15 ml of ethanol, and the mixture was refluxed on a water bath for 3 h. The solvent was evaporated, and the residue was dissolved in benzene–acetone (3:1) and chromatographed. Evaporation of the solvent from the first yellow fraction and crystallization of the residue gave 0.31 g of XXI.

2-Ethylanilino-3-phenothiazone (XXII) and 7-Ethylanilino-3-phenothiazone (XXIII). The method used to prepare XIV and XV was used to obtain these compounds from 0.5 g (2.3 mmole) of I and 2 ml (18 mmole) of monoethylaniline. The yields of XXII and XXIII, respectively, were 0.5 g and 0.1 g.

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