CHEMISTRY OF HETEROCYCLIC QUINONE IMINES. 7*. FORMATION OF O- AND C-DERIVATIVES IN THE REACTION OF PHENOTHIAZINONE-3 WITH PHENOLATES

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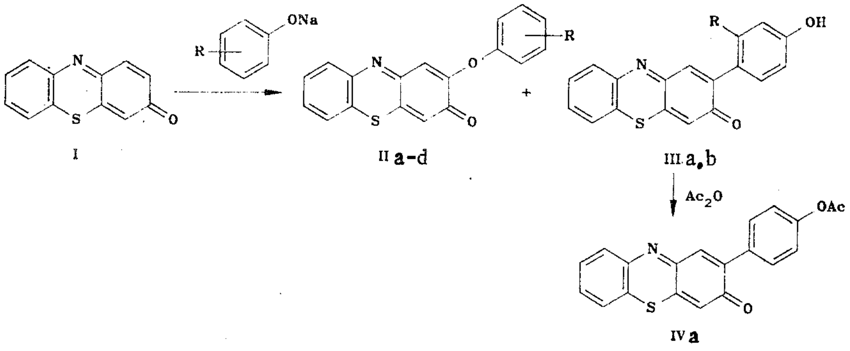
With an activated reagent, the reaction of phenothiazinone-3 with phenol and m-cresol gives, besides 2-aroxy derivatives, also the products of C-substitution, viz., 2-hydroxyarylphenothiazinones-3.

In the reactions of heterocyclic quinone imines with arylamines and thiophenols, only the products of reaction at the nucleophile functional group have been isolated [2, 3], whereas azines are arylated by arylamines to give exclusively p-aminoaryl substituted products [4]. In the reaction of a number of azines and polynitroaromatics with phenolate anion, both C-C' and C-O σ-complexes have been obtained [5, 6]. The selective synthesis of C-C'- or C-O-derivatives has been shown in the reaction of substituted benzoquinones with phenols, depending on the method of reagent activation [7]. The ambidentate nature of phenols and phenolate anions enables us to assume the formation of arylation products also in the case of heterocyclic quinone imines.

The present work is a study of the reaction of phenothiazinone-3 with phenols under conditions of activated reagent and substrate.



a R=H; b R=*m*-CH_3; c R=*o*-CH_3; d R=*n*-CH_3

The combination of an azine structure with a quinone imine segment in phenothiazinone-3 (I) gives a specific reactivity toward phenols that is different from both azines and quinones. Thus, activation of I by conversion to a cation (by H^+ or BF_3) is ineffective in the reaction with phenols. Phenothiazinone-3 reacts with phenolates only in a melt of the respective phenol, and the course of the reaction depends on the type of phenol. Nucleophilic replacement of hydrogen in phenothiazinine-3 occurs only in reaction with the sodium salts of phenol and o-, m-, and p-cresol, from which the products were mainly 2-aroxy derivatives of IIa-d. With I, phenolate and m-cresolate give, besides IIa,b also p-hydroxyarylphenothiazinones-3 (IIIa,b), which in the case of m-cresolate is promoted by favorable location of the methyl and the hydroxy groups; their electron effects have the same sign (^+I and ^+M, respectively). The C-derivatives form as sodium salts which when acidified are converted to III.

Nitrophenolates do not react with phenothiazinone-3 even when fused, as in their reaction with the acridinium cation [4]. With I the sodium salts of 6- and 8-hydroxyquinolines,

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*For communication 6, see [1].

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TABLE 1. Properties of Compounds IIa-d, IIIa,b

Compound	mp, °C (from acetone)	λ_{max}, nm (ethanol)	PMR spectrum, ppm (DMSO-D_6)					Found, %				Empirical formula	Calculated, %			
			protons													
			aliphatic	quinone imine segment		phenolic residue	benzenoid segment of substrate	C	H	N	S		C	H	N	S
				1-H	4-H											
IIa	212—214	500	—	7,04	6,82	7,2—8,2	7,2—8,2	70,3	3,7	4,6	10,5	$C_{18}H_{11}NO_2S$	70,8	8,6	4,5	10,5
IIb	172—174	500	2,40	7,33	6,80	7,0—7,6	7,6—8,1	71,5	4,2	4,5	10,0	$C_{19}H_{13}NO_2S$	71,4	4,1	4,4	10,0
IIc	185—187	500	2,15	7,33	6,55	7,0—7,6	7,6—8,3	71,6	4,2	4,6	9,9	$C_{19}H_{13}NO_2S$	71,4	4,1	4,4	10,0
IId	239—241	500	2,12	7,26	6,73	7,2—7,6	7,6—8,2	71,5	4,0	4,5	10,3	$C_{19}H_{13}NO_2S$	71,4	4,1	4,4	10,0
IIIa	278—280	462	—	7,84	7,11	7,0, d; 7,77, d (J=9,5 Hz)	7,7—8,3	68,8	3,8	4,1	10,3	$C_{18}H_{11}NO_2S \times$ $\times 0{,}5H_2O$	68,7	3,8	4,4	10,2
IIIb	238—240	478	2,1	7,69	7,17	6,5÷7,3	7,5—8,2	71,6	4,5		10,0	$C_{19}H_{13}NO_2S$	71,4	4,1	4,4	10,0

TABLE 2. Mass Spectra of Compounds I, IIa, IIIa, and IVa

Compound	Peak intensity (m/z)*												
	M^+	$[M-H]^+$	$[M-OH]^+$	$[M-SH]^+$	$[M-CO]^+$, Φ_1	$[M-HCO]^+$, Φ_2	$[\Phi-CS]^+$	$[M-CH_2CO]^+$	$[M-CH_3CO]^+$	$[M-C_6H_5]^+$	$[\Phi_1-HCO]^+$	M^{++}	$[C_6H_4S]^+$	$[C_6H_4R]^+$
I	56,6 (213)	—	—	10,0 (180)	100,0 (185)	13,9 (184)	19,3 (141)	—	—	—	—	—	12,8 (108)	16,3 (77)
IIa	100,0 (305)	52,1 (304)	30,3 (288)	11,4 (272)	25,8 (277)	52,1 (276)	10,0 (233)	—	—	10,1 (228)	—	13,4 (152,5)	10,0 (108)	37,8 (77)
IIIa	100,0 (305)	21,6 (304)	—	18,3 (272)	48,3 (277)	32,0 (276)	11,6 (233)	—	—	—	14,0 (248)	6,3 (152,5)	11,8 (108)	10,0 (93)
IVa	28,1 (347)	—	—	15,2 (272)	23,1 (277)	42,2 (276)	—	100,0 (305)	66,3 (304)	—	12,0 (248)	4,0 (173,5)	13,6 (108)	10,0 (135)

*Ion peaks with ⩾10% intensity are shown (except for M^{++}).

3,4-dimethylphenol, ionol, resorcinol, and m-aminophenol give decomposition and autocondensation products of phenothiazinone-3.

The structures of II and III as 2-substituted phenothiazinones-3 were established from the presence in their PMR spectra of singlets of the 1-H and 4-H protons in the 6.55-7.4 ppm region. The hydroxy group in C-substituted derivatives is para to the C-C' bond, and for the 2-hydroxyphenyl derivative this is confirmed by the characteristic doublet of doublets of equivalent protons at 7.0 and 7.77 ppm (J = 9.5 Hz) (see Table 1).

The IR spectra of the C-substituted phenothiazines IIIa,b show the hydroxy absorption band at 3200 cm^{-1}, which is absent from the corresponding acetyl derivatives.

The absorption maxima of II and III in the visible region shift hypsochromically with respect to the unsubstituted phenothiazinone-3. In aqueous alkaline solution the C-derivatives show a reversible bathochromic shift of absorption maximum in the visible, which is related to the change in the conjugation system of the molecule.

Mass spectrometric studies of I, IIa, IIIa, and IV (Table 2) disclosed the fragmentation processes that are typical of quinones, involving elimination of CO (Φ ion) and HCO· (Φ_2) from the molecular ions (M^+) [8]. IIa shows removal of a phenyl radical from M^+, which is specific for the decomposition of ethers [8]. On the other hand, in the case of IIIa and IV the inter-ring bond is not broken [9]. Isomer IIa is distinguished from IIIa by the presence in the mass spectrum by the ion peak with m/z 288 ($[M - OH]^+$), the formation of which is apparently due to the "ortho effect" [10]. The subsequent elimination of a CO molecule from the Φ_2 ion and the release of a ketene molecule and an acetyl radical from M^+ of IV indicate the formation of isomers of III.

EXPERIMENTAL

PMR spectra were obtained on a Perkin Elmer R-12B instrument (60 MHz) in DMSO-D_6, with HMDS internal standard. Electron spectra were obtained on a Specord UV-VIS instrument in ethanol; IR spectra, on a IR-20 instrument in mineral oil; mass spectra, on a MAT-311A instrument at 70 eV ionizing voltage. Purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates.

Reaction of Phenothiazinone-3 with Phenolates. To 2 g (10 mmole) of phenothiazinone-3 (I) dissolved in a 50 ml melt of the phenol was added 15-20 mmole of the sodium phenolate at 80-100°C, with stirring until the TLC spot of the starting compound disappeared.

The reaction mixture was then neutralized with 1 N HCl to weak acidity, and excess phenol was removed by steam distillation. The precipitate of II and III was filtered off, dried, dissolved in 50 ml of chloroform, and chromatographed on a silica gel (40-100 μ) column with ethyl acetate as eluent. In the case of sodium o- and p-cresolates a first orange-red fraction was collected, from which after eluent removal 0.4 g of IIc or IId, respectively, was obtained. For sodium phenolate and m-cresolate, besides the first red-orange zone, a second yellowish-brown fraction is collected, from which were obtained, 0.6 g of IIa, 0.1 g IIIa, and 0.5 f of IIb, 0.1 g of IIIb, respectively.

All the compounds were crystallized from acetone; their properties are given in Table I.

2-(4-Acetoxyphenyl)phenothiazinone-3 (IVa). When 2-hydroxyphenylphenothiazinone-3, IIIa, is boiled in acetic anhydride for 1 h, the acetyl derivative IVa forms in quantitative yield. Mp 230-232°; IR spectrum: 1745 (C=O), 1598, 1616 cm^{-1} (quinone imine vibration). Found: N 4.0%. $C_{20}H_{13}NO_3S$. Calculated: N 4.1%.

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SYNTHESIS AND REACTIVITY OF 10-ALKYLPHENOTELLURAZINES

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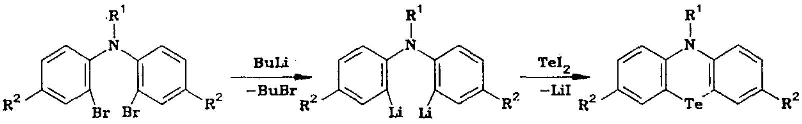
The reaction of N-alkyl-2,2'-dilithium diphenylamines with tellurium diiodide yields derivatives of a new heterocyclic system, phenotellurazine. 10-Alkylphenotellurazines readily form derivatives containing tetra- and tricoordinated tellurium, form complexes with metal salts and rhodium(I) carbonyl chloride, and by bromination and nitration give 3,7-dibromo- or 3-nitro-, 3,7-dinitro, and 1,3,7,9-tetranitro derivatives.

The number of six-membered tricyclic heterocycles containing tellurium that have been described is relatively small: phenoxatellurine [1, 2], phenothiatellurine [3], telluroxanthene [4, 5], telluranthrene [6], and anthracene-10-telluronium perchlorates [7, 8]. Recently we synthesized the first representatives of a new tricyclic system containing tellurium, viz., phenotellurazine [9, 10], the sulfur analogs of which are widely used in medicine as psychotropic agents [11]. Attempts to obtain phenotellurazine by some reactions analogous to those used to synthesize phenothiazines [12] and phenoselenazines [13], by treatment of diarylamines with tellurium metal or tellurium tetrachloride, were unsuccessful. We therefore turned to a very efficient method for constructing a tricyclic system, the reaction of 2,2'-dilithium derivatives of diphenylamines with halides of the respective elements [14].

In the reaction of N-alkyl-2,2'-dilithiumdiphenylamines with tellurium diiodide in an argon atmosphere, the 10-alkylphenotellurazines Ia-d were synthesized in more than 50% yield. The dilithium derivatives were obtained by treating ether solutions of N-alkyl-2,2'-dibromodiphenylamines, IIa-d, with an ether solution of butyllithium at 0°C; in the case of N-alkyl-2,2',4,4'-tetrabromodiphenylamines, at −10°, at which temperature only the bromines in the o-position undergo exchange. It should be noted that recently 10-methyl-5,5-dichlorophenotellurazine was synthesized in 18% yield by the reaction of N-methyl-2,2'-dilithiumdiphenylamine with tellurium tetrachloride [15].



II a-d

I a-d

a, b d $R^1=C_2H_{55}$, c $R^1=CH_3$; a $R^2=H$; b $R^2=CH_3$; c, d $R^2=Br$

The composition and structure of the phenotellurazines I was demonstrated by elemental analysis and PMR spectra. The PMR spectrum of 3,7-dimethyl-10-ethylphenotellurazine (Ib) (Fig. 1) shows successively the triplet and quartet of the ethyl radical, the singlet of the methyls at the 3 and 7 positions, the weakly resolved AB system of the protons at the 1, 2, 8, and 9 positions, and the singlet signal of the aromatic protons at the 4 and 6 positions. The PMR spectrum of 3,7-dibromo-10-ethylphenotellurazine (Id) (Fig. 2) shows the triplet and quartet of the ethyl radical, the doublet of the aromatic protons at the 1 and 9 positions,

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