INTERACTION OF KERAMIDONINES WITH THIOPHENOLS

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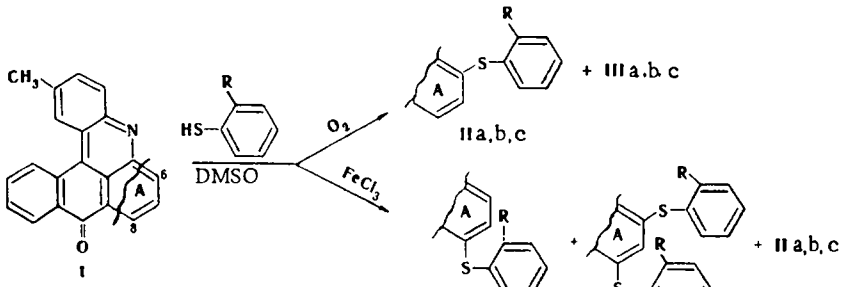
Derivatives of keramidonine (9H-naphth[3,2,1-kl]acridin-9-one) are of practical interest as potential active media in liquid lasers [1]. They are highly susceptible to nucleophilic substitution reactions of the hydrogen atom. We have already examined the reactions of keramidonines with amines [2] and arenesulfinic acids [3]. Here we report a study of the interaction of keramidonines with various thiophenols.

We found that 2-methylkeramidonine (I) reacts with thiophenol, thiosalicyclic acid, and methyl thiosalicylate in dimethyl sulfoxide (DMSO) at room temperature in a stream of oxygen or when air is passed through the reaction mixture, forming mainly 6-arylthiokeramidonines (IIa)-(IIc). In pyridine the reaction takes place only under reflux in the presence of an oxidant, ferric chloride, and again the 6-isomers are predominantly formed. In an inert atmosphere the reaction proceeds only in DMSO, probably as a result of its oxidizing properties [4]. The simultaneous use of ferric chloride and DMSO accelerates the reaction and changes the orientation of the entering group toward the predominant formation of 8-arylthiokeramidonines (IIIa)-(IIIc). Moreover, the reactions with thiophenol and methyl thiosalicylate also formed 6,8-bis(arylthio)keramidonines (IVa) and (IVc), which can be prepared from both 8- and 6-arylthiokeramidonines, but at a greater rate from the 8- than from the 6-isomers.

2-Bromokeramidonine (V) reacts with thiophenol in the same way as 2-methylkeramidonine, but slightly slower. When air is passed through, only 6-phenylthio-2-bromokeramidonine (VI) is formed, in 32% yield, while in the presence of ferric chloride the major products are 8-phenylthio-2-bromokeramidonine (VII) and 6,8-bis(phenylthio)-2-bromokeramidonine (VIII) in 43% and 17% yield, respectively.



II–IV a R = H; b R = COOH; c R = $COOCH_3$ IIIa,b,c IVa,c

The change in the orientation of the entering arylthio group in the presence of ferric chloride in DMSO is apparently due to the complexing properties of iron chloride. We attempted to verify the effect of complexation at the nitrogen atom of the heterocycle by examining the interaction of thiophenol with 2-methylkeramidonine picrate (IX). We found that the picrate reacts more rapidly than the free base. In the presence of atmospheric oxygen the preferential orientation is still at position 6, whereas addition of ferric chloride, as in the case of compound (I), alters the orientation.

The use of ferric chloride does not alter the orientation in the reaction of keramidonines with arenesulfinic acids in DMSO [3] and with thiophenols in pyridine or alcohol. Addition of other Lewis acids, such as $AlCl_3$, does not markedly increase the proportion of the 8-isomer. Ferric chloride and thiophenols are known [5, 6] to form complexes of the type $Fe(SPh)_n^{3-n}$, where n = 1-6, while in DMSO an equilibrium is set up — $FeCl_3$ + 6DMSO $\rightleftarrows$

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TABLE 1. Interaction of 2-Methylkeramidonine (I) with a) Thiophenol, b) Thiosalicyclic Acid, and c) Methyl Thiosalicylate at 20°C

Reactant	Reaction conditions	Reaction time, h	Reaction products, yield, %		
			6-isomer	8-isomer	6,8-bis
a	Methanol, argon	72	—	—	—
a	DMSO, argon	2	38	—	—
a	Pyridine – $FeCl_3 \cdot 6H_2O$	4*	77	5	11
c	Methanol– $FeCl_3 \cdot 6H_2O$	168	45	—	—
a	DMSO, passage of air	2	96	2	—
b		2	62	8	—
c		30	89	2	—
a	(I) was added to the thiophenol–$FeCl_3 \cdot 6H_2O$ complex in DMSO	1	15	60	6
b		1	44	47	—
c		1	13	80	—
a	$FeCl_3 \cdot 6H_2O$ was added to a mixture of the reactants in DMSO	1.5	29	52	16
c		3	22	61	4
a	DMSO, $AlCl_3$	24	72	15	—

*With refluxing.

$[Fe(DMSO)_6]^{3+} + 3Cl^-$ [4]. Obviously only the combined interaction of ferric chloride with thiophenol, dimethyl sulfoxide, and keramidonine modifies the orientation.

The reaction of 2-methylkeramidonine with sodium thiophenolate in DMSO is accompanied by considerable resinification. In this case the reaction is probably complicated by radical processes, like that of keramidonine with alkaline nucleophiles [7].

Thus thiophenols, with the exception of the reactions complicated by the radical processes and complexation phenomena, behave like such weak nucleophiles as arenesulfinic acids and aromatic amines [2]. In the case of arenesulfinic acids the exclusive orientation at position 6 is due not to preliminary protonation, as we assumed earlier [3], but to the low nucleophilicity of the reagent, which is supported by the reaction of tertiary salts of keramidonine with thiophenol. These reagents form the products of substitution of hydrogen mainly at position 6, which has been shown [2] by calculations to have the lowest nucleophilic localization energy. For stronger nucleophiles (aliphatic amines [2], potassium cyanide [8]) the orientation is controlled to a greater extent by the π-electron density distribution, which is a minimum at the 8-carbon atom. The same reason has been suggested for the orientation of nucleophilic substitution in the heterocyclic series [9].

We verified the structures of the 6- and 8-arylthiokeramidonines by synthesis of compounds (IIa), (IIIa), and (IIIb) from the corresponding 6- and 8-chlorokeramidonines and also by conversion of 6-phenylthio-2-methylkeramidonine (IIa) to the sulfone (X) [3], by peracetic acid oxidation using the method of [10]. The intermediate product in the oxidation of aryl sulfide (IIa) is 2-methyl-6-(phenylsulfinyl)keramidonine (XI). We verified the structures of compounds (IIb), (IIc), (IIIc), (VI), and (VII) on the basis of their elemental analyses and molecular weight, and also by comparison of their electronic absorption spectra with those of authentic 6- and 8-isomers. We confirmed the structures of the 6,8-bis(arylthio)keramidonines by synthesis of compound (IVa) from 8-phenylthio-2-methylkeramidonine (IIIa) and from the 6-isomer (IIa).

EXPERIMENTAL

Spectra were recorded on: IR: a UR-20, in KBr tablets; and UV: an SF-16. The elemental compositions of compounds (IIIb) and (XI) were calculated from the accurate mass numbers of the molecular ions (AEI MS-902 mass spectrometer, resolving power ~10,000 direct insertion). The values of R_f were measured on chromatographic paper S, impregnated with 10% solution of α-bromonaphthalene in methanol; the mobile phase was 80% acetic acid saturated with α-bromonaphthalene [11].

Interaction of Keramidonines (I) and (V) with Thiophenols. A suspension of compound (I) or (V) (0.3 g, 1 mmole) and the arylthiol (3 mmole) in DMSO (20 ml) (20 ml pyridine or 100 ml methanol) was stirred at room temperature either in a stream of argon, or while air was passed through the reaction mixture, or in the presence of iron chloride (0.27 g, 1 mmole). Different orders of mixing of the reactants were used (Table 1). The reaction was quenched

TABLE 2. Products of the Interaction of Keramidonines with Thiophenols

Compound	mp, °C (from benzene–ethanol)	R_f	Electronic spectrum in chloroform* λ_{max}, nm (log ε)	Found, %				Formula	Calculated, %			
				C	H	N	S		C	H	N	S
IIa	208—209	0,18	242 (4,59), 286 (4,78), 324 (3,62), 406 (3,93), 480 sh (4,20), 504 (4,26)	80,5	4,3	3,5	7,9	$C_{27}H_{17}NOS$	80,4	4,3	3,5	7,9
IIIa	240—242	0,76	278 (4,75), 428 (4,36), 472 (4,13), 502 (4,12)	80,8	4,5	3,5	8,0	$C_{27}H_{17}NOS$	80,4	4,3	3,5	7,9
IVa	265—267	0,05	290 (4,80), 430 (4,30), 458 sh (4,09), 494 (4,23), 520 (4,23)	77,7	4,2	2,6	12,1	$C_{33}H_{21}NOS_2$	77,5	4,1	2,7	12,5
IIb	196—198	0,57	286 (4,72), 322 sh (3,70), 404 (3,94), 474 (4,11), 498 (4,18)	75,0	3,9	3,2	7,2	$C_{28}H_{17}NO_3S$	75,2	3,8	3,1	7,2
IIIb	305—307	0,90	224 (4,45), 258 sh (4,35), 278 (4,63), 426 (4,30), 468 (4,06), 496 (4,07)			3,0	7,1	$C_{28}H_{17}NO_3S$			3,1	7,2
IIc	170—172	0,25	286 (4,70), 324 sh (3,64), 400 (3,87), 472 (4,12), 500 (4,19)	76,0	4,1	3,0	7,0	$C_{29}H_{19}NO_3S$	75,5	4,1	3,0	6,9
IIIc	213—215	0,77	256 (4,53), 280 (4,79), 426 (4,39), 466 (4,13), 496 (4,12)	75,5	4,0	2,8	6,9	$C_{29}H_{19}NO_3S$	75,5	4,1	3,0	6,9
IVc	236—238	0,14	240 (4,65), 289 (4,78), 433 (4,35), 494 (4,23), 527 (4,27)	70,9	4,0	2,2	10,2	$C_{37}H_{25}NO_6S_2$	70,8	4,0	2,2	10,2
VI†	239—240	0,10	288 (4,97), 402 (4,10), 478 (4,35), 506 (4,37)	66,2	3,3	2,7	6,8	$C_{26}H_{14}BrNOS$	66,7	3,0	3,0	6,8
VII	230—231	0,25	286 (4,79), 428 (4,39), 472 (4,14), 502 (4,15)	66,7	3,0	2,7	6,7	$C_{26}H_{14}BrNOS$	66,7	3,0	3,0	6,8
VIII	310—312	0,04	292 (4,60), 432 (4,07), 460 (3,87), 496 (4,01), 528 (4,05)	67,2	3,2	2,5	11,0	$C_{32}H_{18}BrNOS_2$	66,7	3,2	2,4	11,1

*For (IIIb) in alcohol.
†For compounds (VI), (VII), and (VIII). Found: Br 16.5; 17.0; 13.4%. Calculated: Br 17.0; 17.0; 13.8; respectively.

by pouring the reaction mixture into water. The precipitate was filtered off, washed with water, and dried.

In the runs with thiophenol and methyl thiosalicylate the precipitate was dissolved in chloroform and chromatographed on a silica gel column (elution by benzene). In the case of thiophenol the order of elution was the orange 6,8-bis(phenylthio)keramidonines (IVa) and (VIII), the red 6-phenylthiokeramidonines (IIa) and (VI), the yellow orange 8-phenylthiokeramidonines (IIIa) and (VII), and starting (V). In the case of methyl thiosalicylate the order of elution was 6-(2-methoxycarbonylphenylthio)-2-methylkeramidonine (IIc), 6,8-bis(2-methoxycarbonylphenylthio)-2-methylkeramidonine (IVc), 8-(2-methoxycarbonylphenylthio)-2-methylkeramidonine (IIIc), and starting (I).

In the runs with thiosalicyclic acid the precipitate was treated with refluxing chloroform and freed by filtration from 1,1'-dithiobis[benzene-2-carboxylic acid] with mp 290-292°C (literature 288-290°C [12]). The filtrate was concentrated and chromatographed on a silica gel column. Chloroform eluted reddish brown 6-(2-carboxyphenylthio)-2-methylkeramidonine (IIb); acetone with added ammonia eluted yellow brown 8-(2-carboxyphenylthio)-2-methylkeramidonine (IIIb). IR spectrum of compound (IIIb): 3450 (OH), 1720 (acid C=O), 1635 cm^{-1} (keramidonine C=O). Found: M 447.0920. $C_{28}H_{17}NO_3S$. Calculated: M 447.0929. The yields of the compounds are summarized in Table 1 and their properties appear in Table 2.

6-Phenylthio-2-methylkeramidonine (IIa). A suspension of 6-chloro-2-methylkeramidonine (0.33 g, 1 mmole), thiophenol (0.2 ml, 2 mmole), and 28% KOH (0.1 ml) in ethanol (100 ml) was refluxed for 4 h. The ethanol was stripped off. The residue was dissolved in chloroform and chromatographed on a silica gel column (benzene), giving a red compound (0.26 g, 65%), with IR spectrum identical to that of a sample of (IIa) prepared by interaction of thiophenol with compound (I).

8-Phenylthio-2-methylkeramidonine (IIIa). A suspension of 8-chloro-2-methylkeramidonine (0.23 g, 0.7 mmole) and sodium thiophenolate (0.4 g, 3 mmole) in methanol (30 ml) was refluxed for 4 h and then treated as described above to give a yellow compound (0.24 g, 80%), with IR spectrum identical to that of a sample of (IIIa) prepared from 2-methylkeramidonine and thiophenol.

6,8-Bis(phenylthio)-2-methylkeramidonine (IVa). 1) A suspension of the 8-isomer (IIIa) (0.1 g, 0.25 mmole), ferric chloride (0.07 g, 0.25 mmole), and thiophenol (0.1 ml, 1 mmole) in DMSO (10 ml) was stirred at 20°C for 3 h. The reaction mixture was then poured into water. The precipitate was filtered off, washed with water and with alcohol, and dried. The yield was quantitative.

2) A suspension of the 6-isomer (IIa) (0.4 g, 1 mmole), ferric chloride (0.27 g, 1 mmole), and thiophenol (0.4 ml, 4 mmole) in DMSO (20 ml) was stirred at 20°C for 4 days. The reaction mixture was then poured into water. The precipitate was filtered off, washed with water and with alcohol, and chromatographed on silica gel plates (chloroform). Compound (IVa) (0.03 g, 6%) was isolated from the zone with higher R_f and starting (IIa) from the red zone.

6-(2-Carboxyphenylthio)-2-methylkeramidonine (IIb). A suspension of 6-chloro-2-methylkeramidonine (0.33 g, 1 mmole), thiosalicylic acid (0.5 g, 3 mmole), and 28% KOH (0.1 ml) in ethanol (100 ml) was refluxed for 1 h 30 min. The ethanol was stripped off. The residue was treated with refluxing chloroform and freed by filtration from 1,1'-dithiobis[benzene-2-carboxylic acid] [12]. The filtrate was concentrated and chromatographed on a silica gel column. Benzene eluted the starting product and diethyl ether gave compound (IIb) (0.15 g, 33%). IR spectrum: 3440 (OH), 1725 (acid C=O), 1665 cm^{-1} (quinone C=O).

2-Methylkeramidonine Picrate (IX). This was prepared following [13] by mixing an acetic acid solution of base (I) with alcoholic picric acid. The red needles had mp 256-258°C (from acetic acid). Found: C 61.5; H 3.2; N 10.6%. $C_{21}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated: C 61.8; H 3.1; N 10.7%.

Interaction of 2-Methylkeramidonine Picrate (IX) with Thiophenol. 1) Air was passed through a suspension of picrate (IX) (0.52 g, 1 mmole) and thiophenol (0.2 ml, 2 mmole) in DMSO (20 ml) at 20°C for 1 h. The reaction mixture was then poured into water. The resulting precipitate was filtered off, washed with water, dried, and chromatographed on a silica gel column (benzene) to give the 6-isomer (IIa) (0.34 g, 85%) and the 8-isomer (IIIa) (0.5 g, 12%).

2) The reaction was carried out in the presence of ferric chloride (0.27 g, 1 mmole) for 20 min and gave 6,8-bis(phenylthio)-2-methylkeramidonine (IVa) (0.06 g, 11%), the 6-isomer (IIa) (0.1 g, 25%), and the 8-isomer (IIIa) (0.24 g, 60%).

Oxidation of 6-Phenylthio-2-methylkeramidonine (IIa) by the Method of [10]. A suspension of compound (IIa) (0.20 g) in glacial acetic acid (30 ml) and 30% hydrogen peroxide (15 ml) was stirred at 20°C for 48 h. The reaction mixture was poured into water and neutralized with dilute ammonia. The precipitate was filtered off, washed with water, and dried. It was dissolved in chloroform and chromatographed on silica gel plates. The first red zone gave a compound (0.12 g, 55%) with IR spectrum identical to that of 6-(phenylsulfonyl)-2-methylkeramidonine (X) [3]. The second yellow orange zone gave 2-methyl-6-(phenylsulfinyl)-keramidonine (XI) (0.05 g, 24%), mp 260-262°C (from benzene–ethanol), R_f 0.42. IR spectrum: 1030 cm^{-1} (S=O) [14]. Electronic absorption spectrum, λ_{max} (log ε): 257 (4.49), 285 (4.39), 389sh (3.69), 405 (3.84), 465sh (3.87), 490 nm (3.90). Found: M 419.0979. $C_{27}H_{17}NO_2S$. Calculated: M 419.0955.

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METHYLATION OF 3-ARYLAZOINDAZOLES

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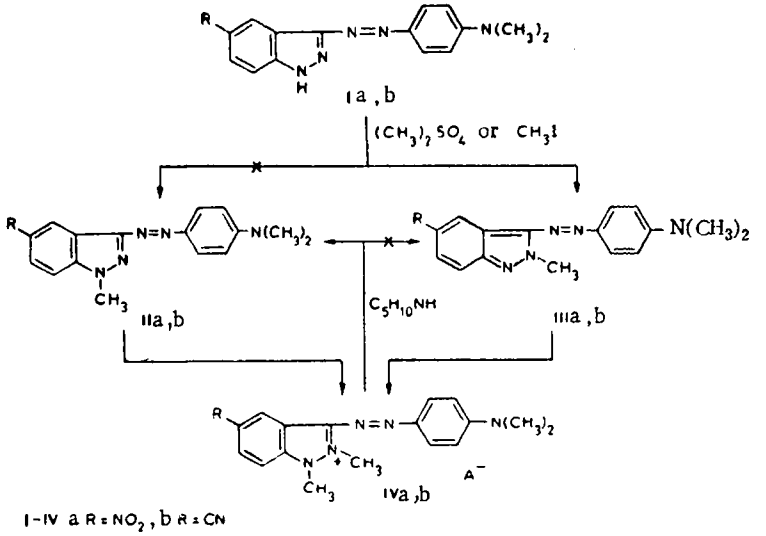
Alkylation of 3-arylazoindazoles represents a possible route to salts of 1,2-dialkyl-3-arylazoindazoles, which are used as cationic dyes. This route is effective if the 3-aminoindazole precursor is available, which is converted into the 3-arylazoindazole by diazotization and azo coupling with an aromatic amine. Although salts of 1,2-dialkyl-3-arylazo-5-nitroindazole have found practical application as dyes, and 3-amino-5-nitroindazole is formed in high yield by the reaction of 5-nitro-2-chlorobenzonitrile with hydrazine hydrate [1], the synthesis of dyes via 3-arylazo-5-nitroindazoles has not been described. They are generally produced by a multistage synthesis of 1,2-dialkyl-5-nitroindazole-3-hydrazones with subsequent oxidative coupling [2, 3].

We have studied the alkylation of 3-arylazo-5-nitroindazoles and of the previously unknown 3-arylazo-5-cyanoindazoles, for example the methylation of 3-(4-dimethylaminophenylazo) derivatives (Ia, b). For identification of the reaction products 1- and 2-methyl-3-arylazoindazoles were synthesized by the alternative route via diazotization of the corresponding N-methyl-3-aminoindazoles and azo coupling with N,N-dimethylaniline.



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