AMINATION OF ANTHRA[1,9-c,d]ISOXAZOL-6-ONES

L. M. Gornostaev, G. F. Zeibert,
and G. I. Zolotareva

UDC 547.786.37'673.5:542.958.3

The behavior of 3,5-dihalo derivatives of anthra[1,9-c,d]isoxazol-6-one with respect to primary and secondary amines was studied. 5-Chloroanthra[1,9-c,d]isoxazol-6-one undergoes amination particularly readily. The products of the reaction of isoxazoles with amines are the corresponding amino derivatives. The amination of 5-chloroanthra[1,9-c,d]isoxazol-6-one in refluxing dimethylformamide (DMF) is accompanied by reductive cleavage of the isoxazole ring and the formation of 1-amino-4-arylaminoanthraquinones. Amination in the 5 position with substitution of a hydride ion takes place primarily in the reaction of 3-chloroanthra[1,9-c,d]isoxazol-6-one with benzylamine of cyclohexylamine, whereas the chlorine in the 3 position is replaced by the action of morpholine or piperidine on the same substrate.

Little study has been devoted to the behavior of anthra[1,9-c,d]isoxazol-6-ones with respect to nucleophilic reagents. Considering the ease of reduction of anthra[1,9-c,d]isoxazol-6-one to 1-aminoanthraquinone [1], we felt it would be interesting to examine the possibilities of the synthesis of various substituted isoxazolones (I), which are potential sources of valuable dyes of the anthraquinone series. We investigated the reaction of 3,5-dihalo-substituted anthra[1,9-c,d]isoxazol-6-ones (Ia-d) with primary and secondary amines. It was found that the amination of Ia-d is realized most successfully in dimethylformamide (DMF) when excess amine (1:2-5) or equimolar ratios of the reagents are used. The reaction proceeded very readily (Table 1) at room temperature or when the components were heated. The reaction also took place in methanol when amines that have high nucleophilicity (piperidine and morpholine) were used.

The amination of anthra[1,9-c,d]isoxazol-6-ones with primary amines was examined in [2]. It was pointed out that a halogen in the 3 position, in contrast to a halogen in the 5 position, is replaced only in the presence of AgNO₃. Under the conditions that we used (see the experimental section) in dimethylformamide (DMF) or methanol replacement of the halogen in both the 3 and 5 position by secondary amines (piperidine and morpholine) was easily accomplished without catalysts. Thus, when piperidine or morpholine is used, the position of the halogen predetermines the pathway of incorporation of the substituent. It was noted that chlorine in the 5 position has a somewhat greater tendency to undergo substitution, and the production of 5-arylaminoanthra[1,9-c,d]isoxazol-6-ones (IIa-g) therefore becomes possible.

The higher tendency of the 5 position to undergo amination is probably explained by the following fact: Direct amination in the 5 position of Ib was observed in the amination of the 3-chloro derivative (Ib) with primary amines, whereas the chlorine atom was not replaced.

Incorporation of the amine in the 3 position was observed in the amination of an isoxazole in which the 5 position was occupied by a p-tolylamino group (IIb). The reaction in this case was carried out in the presence of oxidizing agents, which are known to facilitate replacement of a hydride ion [3].

The high tendency of anthra[1,9-c,d]isoxazol-6-ones to undergo nucleophilic substitution is probably explained by the formation of a stable (as a consequence of the development of aromatic character in the central ring of the anthrone) transition state, which may be additionally stabilized by an intramolecular hydrogen bond.

In [2] it was noted that the products of amination in the 3 position are unstable compounds that are inclined to undergo conversion with reduction of the heteroring and are therefore not isolated in free form, despite the ease with which they are formed.

TABLE 1. Synthesis and Characteristics of Aminoanthra[1,9-c,d]-isoxazol-6-ones[a]

Compound	Temp. (°C); time (h); amt. solvent (ml)/0.01 mole Ia-d	mp, °C	λ_{max}, nm (lg ε)	N found, % (Cl, %)	Empirical formula	N calc., % (Cl, %)	Yield, %
IIa	80; 2; 40	206	261 (4,37); 498 (4,22); 526 (4,26)	8,57	$C_{20}H_{12}O_2N_2$	8,97	70,5
IIb	80; 2; 40	213—214	265 (4,40); 504 (4,19); 528 (4,24)	8,47 8,76	$C_{21}H_{14}O_2N_2$	8,58	68,0
IIc	80; 2; 40	165—166	262 (4,39); 496 (4,26); 512 (4,28)	8,52 8,42	$C_{21}H_{14}O_2N_2$	8,56	77,0
IId	80; 2; 40	213—214	272 (4,27); 490 (4,11); 515 (4,16)	7,82	$C_{20}H_{11}O_2N_2Cl$	8,08	74,0
IIe	80; 2; 40	208—209	273 (4,31); 490 (4,13); 519 (4,17)	6,9	$C_{20}H_{11}O_2N_2Br$	7,16	57,0
IIf	80; 2; 40	186—187	265 (4,35); 491 (4,20); 515 (4,25)	8,22	$C_{21}H_{14}O_3N_2$	8,18	59,0
IIg	80; 2; 40	199—200	261 (4,45); 500 (4,16); 512 (4,24)	7,68 7,76	$C_{22}H_{16}O_3N_2$	7,80	78,5
IIh	60; 2; 80	151—153	262 (4,38); 495 (3,98); 530 (4,00)	9,13	$C_{19}H_{16}O_2N_2$	9,21	76,0
IIi	0; 2; 80	215—216	260 (4,55); 500 (4,20); 535 (4,27)	7,45 (9,71; 9,59)	$C_{20}H_{17}O_2N_2Cl$	7,94 (10,07)	70,0
IIj	0; 2; 80	190—191	259 (4,55); 495 (4,19); 530 (4,20)	7,28 (9,66; 9,64)	$C_{21}H_{13}O_2N_2Cl$	7,76 (9,84)	50,0
IIIa	64; 3—4; 150	133—134	265 (4,53); 543 (4,50)	8,98	$C_{19}H_{16}O_2N_2$	9,21	65,3
IIIb	64; 2—3; 150	129—130	263 (4,51); 518 (4,45)	9,15	$C_{18}H_{14}O_3N_2$	9,04	80,0
IIIc	64; 3; 150	189—190	255 (4,52); 490 (4,33); 520 (4,43)	10,60 10,37	$C_{25}H_{21}O_2N_3$	10,63	65,7
IIId	64; 3; 120	196—197	256 (4,50); 488 (4,33); 520 (4,42)	10,52 10,67	$C_{24}H_{19}O_3N_3$	10,58	50,5
IIIe	20; 3; 100	195—196	258 (4,52); 490 (4,23); 519 (4,31)	9,82 9,61	$C_{27}H_{19}O_2N_3$	10,07	56,6
IIIf	20; 0,5; 80	196—197	252 (4,48); 479 (4,29); 510 (4,38)	11,98 12,07	$C_{21}H_{15}O_2N_3$	12,31	68,9
IIIg	20; 0,5; 80	199—200	254 (4,46); 489 (4,33); 519 (4,42)	11,80 11,79	$C_{22}H_{17}O_2N_3$	11,83	90,8
IIIh	60; 0,5; 80	171—172	253 (4,39); 486 (4,24); 515 (4,33)	11,40 11,62	$C_{22}H_{17}O_2N_3$	11,83	66,0
IIIi	64; 4; 160	202	258 (4,50); 484 (4,36); 520 (4,45)	10,71 10,64	$C_{26}H_{23}O_2N_3$	10,26	80,0 (67) b
IIIj	64; 6; 120	206—207	262 (4,58); 485 (4,40); 518 (4,49)	10,71	$C_{25}H_{17}O_2N_3$	10,22	0'69
IIIk	40; 0,5; 80	185—186	254 (4,57); 475 (4,36); 510 (4,43)	9,91 9,51	$C_{27}H_{25}O_2N_3$	9,93	67,3
IIIl	60; 2; 100	179—180	254 (4,52); 478 (4,33); 506 (4,40)	9,83	$C_{28}H_{21}O_2N_3$	9,74	66,0
IIIm	60; 2; 80	212—213	256 (4,55); 494 (4,31); 510 (4,39)	11,76 11,52	$C_{22}H_{17}O_2N_3$	11,83	80,4
IIIn	45; 1; 80	233—234	254 (4,54); 480 (4,36); 510 (4,43)	11,10 10,96	$C_{23}H_{19}O_2N_3$	11,38	87,9
IIIo	50; 1; 80	183—184	254 (4,51); 480 (4,33); 510 (4,40)	11,25 11,16	$C_{23}H_{19}O_2N_3$	11,38	76,9

[a] Compounds IIa-h were obtained by amination of Ia, IIi-j and IIIa,b were obtained by amination of Ib, IIIc-h were obtained by amination of Ic, and IIIi-o were obtained by amination of Id.
[b] The yield of IIIi obtained by oxidative alkylamination of IIb is presented in parentheses.

Compounds IIIa-o were isolated preparatively in high yields under the conditions that we used. We noted that these compounds are readily transformed in light or when they are heated in solvents, but they are not converted to 1-amino-2-R-aminoanthraquinones. The problem of the structures of the products of the transformation of IIIa-o requires a special study (see scheme on following page).

We also observed that the amination of Ia by heating is accompanied by reduction of the heteroring; the corresponding 1-amino-4-arylaminoanthraquinones were isolated in preparative yields when the reaction of
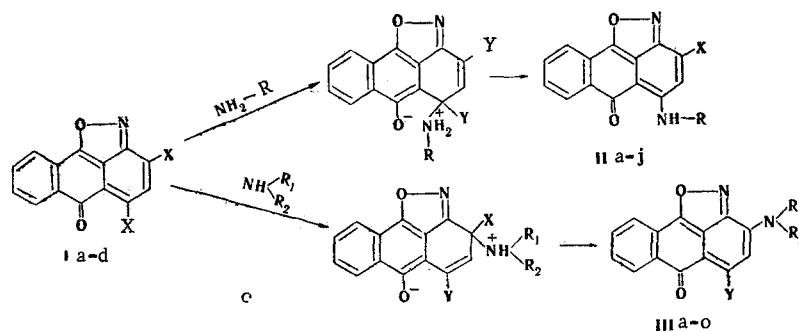
I a X=H, Y=Cl; I b X=Cl, Y=H; I c X=Br, Y=NH—Ph; I d X=Br, Y=NH-*p*-Ph—CH₃;
II a R=C₆H₅, X=H; II b R=*p*-C₆H₄—CH₃, X=H; II c R=*m*-C₆H₄—CH₃, X=H;
II d R=*p*-C₆H₄—Cl, X=H; II e R=*p*-C₆H₄—Br, X=H; II f R=*m*-C₆H₄—O—CH₃, X=H;
II g R=*p*-C₆H₄—O—C₂H₅, X=H; II h R=(CH₂)₅, X=H; II i R=CH(CH₂)₅, X=Cl;
II j R=CH₂—C₆H₅, X=Cl; III a Y=H, R₁R₂=(CH₂)₅; III b Y=H,
R₁R₂=(CH₂)₂—O—(CH₂)₂; III c Y=NH—C₆H₅, R₁R₂=(CH₂)₅; III d Y=NH—C₆H₅,
R₁R₂=(CH₂)₂—O—(CH₂)₂; III e Y=NH—C₆H₅, R₁=H, R₂=CH₂—C₆H₅; III f
Y=NH—C₆H₅, R₁=H, R₂=CH₃; III g Y=NH—C₆H₅, R₁=R₂=CH₃; III h Y=NH—C₆H₅,
R₁=H, R₂=CH₂—CH₃; III i Y=*p*-NH—C₆H₄—CH₃, R₁R₂=(CH₂)₅; III j
Y=*p*-NH—C₆H₄—CH₃, R₁R₂=(CH₂)₂—O—(CH₂)₂; III k Y=*p*-NH—C₆H₄—CH₃, R₁=H,
R₂=CH(CH₂)₅; III l Y=*p*-NH—C₆H₄—CH₃, R₁=H, R₂=CH₂—C₆H₅; III m
Y=*p*-NH—C₆H₄—CH₃, R₁=H, R₂=CH₃; III n Y=*p*-NH—C₆H₄—CH₃, R₁=R₂=CH₃; III o
Y=*p*-NH—C₆H₄—CH₃, R₁=H, R₂=CH₂—CH₃

Ia with arylamines was carried out in refluxing DMF (see the experimental section). Moreover, the cycliza-
tion of 1-azido-4-chloroanthraquinone to isoxazolone Ia and arylamination of the latter have been success-
fully combined; the final products in this case were also 1-amino-4-arylaminoanthraquinones (IVa-h).

The structures of the amination products were thus confirmed by their reduction. In addition, IIa,b
were obtained by alternative synthesis by cyclization of the corresponding 1-azidoanthraquinones and had
identical characteristics. Absorption of a carbonyl group was observed in the IR spectra of Ic,d, IIa-j, and
IIIa-o at 1670-1680 cm^{-1}, and the band of a heterocyclic C=N bond was observed at 1620-1630 cm^{-1}.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord 75-IR spectrometer. The
electronic spectra of solutions of the compounds in dioxane were recorded with a Specord UV-vis spectro-
photometer. The course of the reaction in all cases was monitored by thin-layer chromatography (TLC) on
Silufol UV-254 plates.

Anthra[1,9-c,d]isoxazol-6-ones Ia,b were synthesized by known methods [4].

Starting Isoxazolones (Ic,d). A 0.05-mole sample of 1-amino-4-arylamino-2-bromoanthraquinone was
diazotized in 500 ml of acetic acid with 0.06 mole of freshly distilled amyl nitrite with stirring at room tem-
perature. A 0.06-mole sample of NaN₃ was added to the filtered solution of the diazonium salt, and the mix-
ture was allowed to stand for 30 min. It was then diluted with 1 liter of water, and the precipitated 1-azido-2-
bromo-4-arylaminoanthraquinone was removed by filtration, dried, and refluxed in 100-120 ml of toluene for
1.5-2 h. This procedure gave Ic in 70% yield and Id in 72% yield. Recrystallization from toluene gave pure Ic
with mp 212°C. Found: N 7.5%. Calculated: N 7.2%. Recrystallization from toluene gave pure Id with mp
245°C. Found: N 6.7%. Calculated: N 6.9%. The alternative synthesis of IIa,b was carried out similarly.

Anthra[1,9-c,d]isoxazol-6-one Derivatives (IIa-g). A 0.01-mole sample of 5-chloroanthra[1,9-c,d]
isoxazol-7-one was stirred with 0.02 mole of arylamine in DMF (see Table 1 for the temperature, time, and
amount of solvent for this and the subsequent experiments). After the reaction mixtures were cooled to
0-5°C, IIa-g were removed by filtration and recrystallized from ethanol.

Oxidative Alkylamination of Isoxazolone IIb. A 0.005-mole sample of isoxazolone IIb was stirred for 5
h in a solution of 10 ml of piperidine and 5 ml of DMF at room temperature in the presence of 4 g of pulver-
ized KNO₃, after which the reaction mixture was maintained under the usual conditions for 50 h. It was then
diluted with water, and final product IIIi was removed by filtration and recrystallized from ethanol—dioxane
(10:1).

Anthra[1,9-c,d]isoxazol-6-one Derivatives (IIIa-d,i,j). A 0.02-mole sample of isoxazolone Ib-d was
refluxed with 0.05 mole of the amine (a tenfold excess of morpholine was used for the preparation of IIIb) in
methanol, after which the mixture was cooled to 0-5°C, and the reaction products were removed by filtration

and recrystallized from ethanol—dioxane (10:1).

3,5-Diaminoanthra[1,9-c,d]isoxazol-6-ones (IIIe-h,k-o). A 0.01-mole sample of the isoxazolone (Ib-d) was stirred in DMF with 0.05 mole of the amine, after which the mixture was maintained at 0-5°C for 10-15 h. The final products were removed by filtration and recrystallized from ethanol—dioxane (10:1).

Reductive Arylamination of 5-Chloroanthra[1,9-c,d]isoxazol-6-one (Ia). A 0.01-mole sample of Ia was refluxed with 0.015 mole of arylamine in 30-50 ml of DMF for 1.5-2 h, after which the mixture was cooled to 100-110°C and treated with 20-30 ml of water heated to 50-60°C. The resulting suspension was cooled to 5-10°C and filtered, and the reaction products were recrystallized from ethanol or acetic acid. This procedure gave 1-amino-4-(R-phenylamino)anthraquinones IVa-h in the following yields: IVa, R = H, 80%; IVb, R = p-CH$_3$, 95%; IVc, R = o-CH$_3$, 89%; IVd, R = 2,4-di-CH$_3$, 71%; IVe, R = p-Br, 97%; IVg, R = m,o-CH$_3$, 80%; IVh, R = p,o-C$_2$H$_5$, 83%.

Arylamination of 1-Azido-4-chloroanthraquinone. This process was carried out in complete analogy with the preceding procedure using an equimolar amount of 1-azido-4-chloroanthraquinone in place of isoxazolone IA. 1-Amino-4-arylaminoanthraquinones IVa-h were obtained in 70-80% yields. Compounds IV had spectral characteristics that were similar to the literature values [5].

LITERATURE CITED

1. L. Gattermann and H. Rolfes, Ann., 425, 144 (1921).
2. A. M. Galushko and N. S. Dokunikhin, Zh. Org. Khim., 15, 575 (1979).
3. L. V. Éktova, R. P. Shishkina, and E. P. Fokin, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim., No. 5, 126 (1978).
4. A. Schaarschmidt, Ber., 49, 1635 (1916).
5. F. Ya. Fain, Tables of the Electronic Spectra of Anthraquinone and Its Derivatives [in Russian], Khimiya, Moscow (1970), p. 67.

REACTION OF SULFOLENE OXIDES WITH ACYL
CHLORIDES AND CHLORO ETHERS

L. A. Mukhamedova, L. I. Kursheva,
and F. S. Khasyanzyanova

The reaction of sulfolene and 3-methylsulfolene oxides with acetyl chloride, benzoyl chloride, and chlorodimethyl and chloromethyl ethyl ethers was studied. It is shown that sulfolene oxides are rather stable in acidic media and undergo ring opening only when they are heated above 100°C under pressure. In the case of the unsymmetrical 3-methylsulfolene oxide the oxide ring undergoes opening to a greater extent on the side of the carbon atom that bears the alkyl substituent.

The oxide rings of sulfolene oxides are exceptionally stable in acidic media, as one can judge from the method used to prepare them [1]. The aim of the present research was to study the reactions of sulfolene oxide (I) and 3-methylsulfolene oxide (II) with carboxylic acid chlorides and chloro ethers in the presence of acid catalysts and to establish the order of addition of the reagents to unsymmetrical oxide II.

Whereas the reactions of olefin and cyclo-olefin oxides with chlorine-containing reagents proceed rather readily [2], the reactions of sulfolene oxides I and II with acetyl chloride, benzoyl chloride, and chlorodimethyl and chloromethyl ethyl ethers could be realized only under pressure by heating above 100°C in absolute benzene. The characteristics of III-X and XVII are presented in Table 1.