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ALKYLATION OF N-(1-ANTHAQUINONYL)UREAS AND THEIR CYCLIZATION TO ANTHRA[1,2-d]IMIDAZOLINONES

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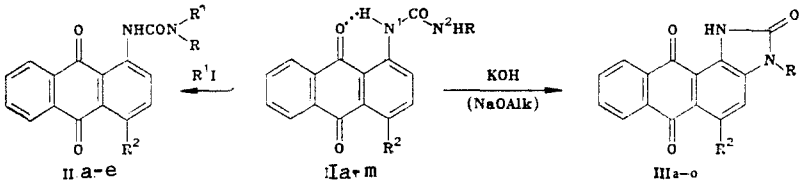
N^1-(1-Anthraquinonyl)-N^2-arylureas in DMSO in the presence of bases form N-anions which cyclize to anthra[1,2-d]imidazolinones, and in the presence of alkyl halides give the N^2-alkyl derivatives. Anions of N^1-(1-anthraquinonyl)-N^2-alkylureas are less stable, and are rapidly converted into 1-aminoanthraquinone.

Anthraquinonylureas are of interest from the practical point of view as dyestuffs [1, 2], pesticides [3], and as additives to lubricating oils which increase their stability to heat and radiation [4]. The chemical properties of these compounds are unknown. The aim of the present investigation was to examine the properties of the newly-synthesized N^1-(1-anthraquinonyl)-N^2-aryl (and alkyl)ureas (Ia-m) [3] in basic media. Ureas are known to behave as mono- or dibasic NH-acids on treatment with bases [5]. Some N-substituted aminoanthraquinones are also known to form N-anions [6, 7].

Addition of an equimolar amount of potassium hydroxide to a solution of the arylureas (Ia-k) in DMSO at 20-25°C results in a considerable deepening of the color of the solution, which remains unchanged in the presence of excess alkali, indicating that the urea is monoionized. In considering the potential for ionization of one of the two NH-acidic centers in the ureas (Ia-k), preference should be given to the HN^2Ar group, since the N^1H grouping is involved in intramolecular hydrogen bonding with the quinone oxygen [3], and is therefore less acidic (cf. [6]). In order to confirm this mode of ionization, we examined the alkylation of the ureas (Ia) and (Ib) in basic media.



IIa-e IIa-m IIIa-o

I a–d R^2=H, e-h R^2=OH, i R^2=Cl, j R^2=4-$OC_6H_4C(CH_3)_3$; a,e,i,j R=C_6H_5, b,f R=3-ClC_6H_4, c,g R=4-ClC_6H_4, d R=1-naphthyl h R=3,4-$Cl_2C_6H_3$; l k R^2= =4-$OC_6H_4C(CH_3)_3$, l,m R^2=H; k R=4-ClC_6H_4, l R=C_4H_9, m R=CH_3

Addition of methyliodide to a solution of the N-anion of urea (Ia) in DMSO resulted even at room temperature in the formation of the N^2-methylurea (IIa). Ureas (Ia) and (Ib) were fully alkylated in dioxane at 60°C in the presence of solid potassium hydroxide to give the N^2-alkylureas (IIa-d) (Table 2). The structures of these products were confirmed spectroscopically, and by the direct synthesis of (IIa) from 1-aminoanthraquinone and N-methyl-N-phenylcarbamoyl chloride.

It would be expected that in the N^2-alylated ureas (Il, m) the acidity of the N^2H group would be reduced as compared with the aryl derivatives (Ia-m) [5, 6], so that either of the NH groups could become ionized. Comparison of the UV spectra of the anthraquinonylureas (Ia, b, l) and (IIb, e) with their anions showed that ionization of the N^2H group (arylureas (Ia, b)) resulted in a shift of the long-wavelength maximum by $\Delta\lambda \approx 130$ nm (Table 1),

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TABLE 1. Long-Wavelength Absorption of Some Ureas (I) and (II) and Their Anions (in brackets)

Compound	λ_{max}, nm
Ia	440 (570)
Ib	440 (568)
Im	448 (492)
IIb	448 (641)
IIc	450 (665)

TABLE 2. Properties of Compounds Obtained

Compound	R	R^1 (R^3)	R^2	Empirical formula	mp, °C	Yield, %
IIa	C_6H_5	CH_3	—	$C_{22}H_{16}N_2O_3$	162...167	70
IIb	C_6H_5	C_2H_5	—	$C_{23}H_{18}N_2O_3$	164...169	76
IIc	C_6H_5	C_4H_9	—	$C_{25}H_{22}N_2O_3$	149...152	86
IId	3-ClC_6H_4	CH_3	—	$C_{22}H_{15}ClN_2O_3$	193...196	83
IIe	C_4H_9	CH_3	—	$C_{20}H_{20}N_2O_3$	135...138	25
IIIa	C_6H_5	—	H	$C_{21}H_{12}N_2O_3$	343...344	59
IIIb	3-ClC_6H_4	—	H	$C_{21}H_{11}ClN_2O_3$	333...335	67
IIIc	4-ClC_6H_4	—	H	$C_{21}H_{11}ClN_2O_3$	>350	77
IIId	1-naphthyl	—	H	$C_{25}H_{14}N_2O_3$	292...295	51
IIIe	C_6H_5	—	OH	$C_{21}H_{12}N_2O_4$	>350	69
IIIf	3-ClC_6H_4	—	OH	$C_{21}H_{11}ClN_2O_4$	>360	66
IIIg	4-ClC_6H_4	—	OH	$C_{21}H_{11}ClN_2O_4$	>350	70
IIIh	3,4-$Cl_2C_6H_3$	—	OH	$C_{21}H_{10}Cl_2N_2O_4$	>350	60
IIIi	C_6H_5	—	Cl	$C_{21}H_{11}ClN_2O_3$	355...357	63
IIIj	C_6H_5	—	$OC_6H_4C(CH_3)_3$	$C_{31}H_{24}N_2O_4$	>360	56
IIIk	C_6H_5	—	OCH_3	$C_{22}H_{14}N_2O_4$	265...270	75
IIIl	4-ClC_6H_4	—	OCH_3	$C_{22}H_{13}ClN_2O_4$	298...300	50
IIIm	C_6H_5	—	OC_2H_5	$C_{23}H_{16}N_2O_4$	279...281	69
IIIn	C_6H_5	—	$OCH(CH_3)_2$	$C_{24}H_{18}N_2O_4$	274...279	51
IIIo	C_6H_5	—	$OCOCH_3$	$C_{23}H_{14}N_2O_5$	>320**	93
IIIp	C_6H_5	(CH_3)	H	$C_{22}H_{14}N_2O_3$	264...266	72
IIIq	C_6H_5	($CH_2C{\equiv}CH$)	H	$C_{24}H_{14}N_2O_4$	196...198	73
IIIr	C_6H_5	(CH_3)	OH	$C_{22}H_{14}N_2O_4$	248...249	40

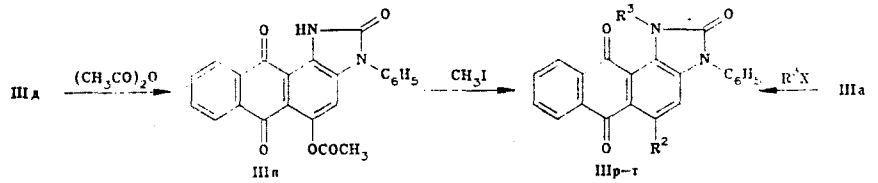
*Compounds (IIa-d) and (IIIp, r) were crystallized from acetonitrile, (IIIa-1,o) from dimethylformamide, (IIe) from ethanol, (IIIq) from benzene, and (IIIk-n) from a 1:3 mixture of dioxane and acetonitrile.
**Decomposed on melting.

whereas when the N^1H group was ionized (arylalkylureas (IIb, e)), the $\Delta\lambda$ value was ≈200 nm. In the case of the alkylurea (Il), this shift immediately following the addition of alkali was 46 nm, suggesting ionization of the N^2H group. After a few minutes, however, a new maximum appeared (690 nm), the position of which, and the appearance of the curve as a whole, indicated the formation of the N-anion of 1-aminoanthraquinone [7]. In fact, following dilution of the mixture with water, 1-aminoanthraquinone was the sole product (by TLC). In view of the low stability of the alkylureas (Il, m) in alkaline solution, complications also arose on alkylation. The reaction with methyl iodide was possible only with (Il), giving the N^2-methylurea (IIe) in low yield. According to TLC, the reaction mixture contained the starting urea (Il), 1-aminoanthraquinone, and its alkylation products, Alkylureas such as (Il) are therefore ionized at N^2H, but the stability of the resulting anions is much lower than in the arylureas (Ia-k). In turn, the latter remain unchanged in DMSO for only one hour, after which time cyclization to anthra[1,2-d]imidazolinones (IIIa-k) becomes appreciable (Table 2). After a few days, the main products are (IIIa-k), 1-amino-anthraquinone also being present in the mixtures but only in small amounts. The IR spectra of (IIIa-k) showed absorption for the heterocyclic carbonyl group at 1730-1750 cm^{-1} [8, 9]. The quinone carbonyl groups in the imidazolinones (IIIa-d, i-k) were seen as a single band at 1660-1680 cm^{-1} ([8]), and the 5-hydroxy compounds (IIIe-h) showed a second for the C=O group absorption at 1630-1640 cm^{-1} attributed to the intramolecular hydrogen bond. In the PMR spectrum of the imidazolinone (IIIa) no signals were present at low field for the protons at $C(_2)$ and one of the NH groups, such as are characteristic of N-(1-anthraquinonyl)ureas [3]; in addition to the signals for the protons of the phenyl substituent and the unsubstituted anthraquinone ring, two doublets were present for 3-H and 4-H at 7.34 and 8.07 ppm, indicating 1,2-disubstitution in the anthraquinone moiety of the molecule.

From these results, a method has been developed for the synthesis of the anthraimidazolinones (IIIa-k) from the ureas (Ia-k) in the presence of basic reagents [10]. In aqueous media, the best results were obtained with KOH solutions in concentrations of 5-15%. Increasing the concentration to 50%, or using sodium hydroxide resulted in the buildup of 1-aminoanthraquinone in the mixture. The anthraimidazolinones (IIIa-k) were formed in DMSO in the presence of solid alkali, although the reaction times were considerably longer, but the use of sodium alkoxide in the appropriate alcohol substantially accelerated the reaction and side reactions were avoided. Only in the case of (Ij, k), which carry a p-tert-butyl group in the 4-position of the anthraquinone, did the use of alkoxides result in concurrent cyclization and transesterification to give the 5-alkoxanthraimidazolinones (IIIl-n). Cyclization of anthraquinonylureas in the presence of alkalis and alkoxides also occurs in other solvents (DMF, pyridine, and dioxane).

The usual method of synthesis of anthraimidazoles is by reacting o-diaminoanthraquinones with carbonyl compounds [9, 11]. In the benzene series, N^1-benzyloxy-N^2-phenylureas are known to cyclize to benzimidazolin-2-ones in the presence of lead tetraacetate [12]. The hitherto unknown intramolecular cyclization of the ureas (Ia-k) to the anthraimidazolinones (IIIa-n) can obviously be regarded as a special case of oxidative amination, characteristic of hydroxy- and aminoanthraquinones, in which the possible contribution of ana-quinoloid structures in the pesence of base has been suggested [11]. The oxidant may be atmospheric oxygen, the starting quinone, or the solvent (when the reaction is carried out in DMSO).

The anthraimidazolinones (IIIa-n) are high-melting, crystalline solids which are sparingly soluble in organic solvents, and are stable to acids. Treatment of the solutions in DMSO or DMF with bases results in ionization, accompanied by a bathochromic shift of the long-wavelength absorption maximum by approximately 100 nm.



We have also examined the acylation and alkylation of the imidazolinones. In the case of (IIIa), it was found that the anthraquinonylimidazolinone ring is stable towards acylating agents under a range of conditions, including esterification of the 1-hydroxy group of the anthraquinone [11]. For example, boiling the 5-hydroxy compound (IIIe) with acetic anhydride gives only the O-acetyl derivative (IIIo), the IR spectrum of which shows absorption for ν_{OCOCH_3} and ν_{NH}. Alkylation of the anthraimidazolinones occurs readily. For example, treatment of the N-anion of the imidazolinone (IIIa) with methyl iodide and propargyl chloride gives high yields of the 1-alkylanthraimidazolinones (IIIp, q) (Table 2). Alkylation of the acetoxy-compound (IIIo) with methyl iodide in the presence of alkali results in deacetylation to give the 1-methyl-5-hydroxy-compound (IIIr).

EXPERIMENTAl

IR spectra were obtained on a UR-20 spectrometer in KBr disks, and UV spectra on a Specord UV-VIS in chloroform, the spectra of the anions being obtained in DMSO with the addition of an equimolar amount or a three fold excess of 5% aqueous KOH and a concentration of the NH-compound of 10^{-3} mole/liter. PMR spectra were obtained on Varian A56/60A (60 MHz) and Bruker WP-200SY (200 MHz) spectrometers (internal standard HMDS). The reactions were followed by TLC on Silufol UV-254 plates (eluent chloroform). The properties of the products are given in Table 2. The elemental analyses for C, H, N, and Cl were in agreement with the calculated values.

N^1-(1-Anthraquinonyl)-N^2-methyl-N^2-phenylurea (IIa). A. A mixture of 1 g (2.92 mmole) of the urea (Ia), 0.45 g (8 mmole) of powdered potassium hydroxide, and 3 ml of methyl iodide in 55 ml of dioxane was stirred for 2 h at 60°C, then cooled and the inorganic solid filtered off. The filtrate was evaporated, and the residue triturated with pentane and recrystallized. IR spectrum: 1650, 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 302 (3.92), 443 nm (3,83). PMR spectrum: 3.40 (s, 3H, N–CH_3), 7.23-8.30 (m, 11H arom.), 9.07 (d.d, 1H, anthraquinone 2-H, $J_{2,3}$ = 8 Hz, $J_{2,4}$ = 3 Hz), 11.55 ppm (s, 1H, NH).

B. A mixture of 1g of N-methylaniline and 3 g of phosgene in 10 ml of toluene was stirred for 4 h at 20°C, and the toluene distilled off. The residue was dissolved in 10 ml of pyridine, a suspension of 1 g of 1-aminoanthraquinone in 20 ml of pyridine added dropwise, and the mixture heated for 20 h at 100°C. After cooling, the mixture was poured into a mixture of ice and conc. HCl (1:1). The solid was filtered off and chromatographed (silica gel, eluent chloroform) to give 0.5 g of product. The melting point and IR spectra of the products obtained by methods A and B were identical.

Ureas (IIb-d) were obtained by method A from ureas (Ia, b) with ethyl, butyl, or methyl iodide.

N^1-(1-Anthraquinonyl)-N^2-methyl-N^2-butylurea (IIe) was obtained similarly, from (I1) and methyl iodide at 100°C, and purified by chromatography (silica gel, eluents chloroform and benzene). IR spectrum: 1640, 1670 (C=O); 2860, 2870, 2925, 2955 cm^{-1} (aliph. C—H). PMR spectrum: 0.77-1.83 (m, 7H aliph.), 3.13 (s, 3H, N—CH_3), 3.48 (t, 2H, N—CH_2, J = 7 Hz), 7.28-8.33 (m, 6H anthraquinone), 9.03 (d.d, 1H, anthraquinone 2-H, $J_{2,3}$ = 9 Hz and $J_{2,4}$ = 1.5 Hz), 11.98 ppm (s, 1H, NH).

2,3-Dihydro-3-phenyl-1H-anthra[1,2-d]imidazole-2,6,11-trione (IIa). A mixture of 2.6 g (7.6 mmole) of the urea (Ia) and 8 ml (7.6 mmole) of 5% aqueous KOH in 220 ml of DMSO was kept for seven days at 20-25°C, then diluted with water to a volume of 1 liter. The solid was filtered off, dried, and recrystallized. IR spectrum: 1680, 1745 (C=O), 3290 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 425 nm (4.00). PMR spectrum: 7.34 (d, 1H, anthraimidazolinone 4-H, $J_{4,5}$ = 7 Hz), 7.54 (m, 5H, N—C_6H_5), 7.81 (m, 2H, 8-H and 9-H), 8.07 (d, 1H, 5-H, $J_{5,4}$ = 7 Hz), 8.31 (m, 2H, 7-H and 10-H), 9.84 ppm (s, 1H, NH).

The anthraimidazolinones (IIIb, d-f, h, j) were obtained similarly from ureas (Ib, d-f, h, j).

2,3-Dihydro-3-(4-chlorophenyl)-1H-anthra[1,2-d]imdazole-2,6,11-trione (IIIc). A mixture of 1.86 g (4.9 mmole) of the urea (Ic) and a freshly-prepared solution of sodium methoxide (from 0.43 g of sodium and 7.5 ml of methanol) in 200 ml of DMSO was stirred for 7 h at 20°C, and worked up as for (IIIa). IR spectrum: 1670, 1745 (C=O), 3360 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 426 nm (3.79).

The anthraimidazolines (IIIb, d-f, h, j) were obtained similarly from ureas (Ig, i, j, k). Anthraimidazolines (IIIm, n) were obtained similarly from (Ij) and sodium ethoxide or isopropoxide.

2,3-Dihydro-3-phenyl-5-acetoxy-1H-anthra[1,2-d]imidazol-2,6,11-trione (IIIo). A suspension of 1.36 g (3.82 mmole) of the anthraimidazoline (IIIe) in 90 ml of freshly-distilled acetic anhydride was boiled for 2 h 30 min. After cooling, the solid was filtered off, dried and recrystallized. IR spectrum: 1660, 1740, 1770 (C=O), 3340 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 425 nm (4.05).

2,3-Dihydro-1-methyl-3-phenylanthra[1,2-d]imidazole-2,6,11-trione (IIIp). A mixture of 0.8 g (2.35 mmole) of the anthraimidazoline (IIIa), 0.4 g (7.14 mmole) of finely-ground KOH, and 5 ml of methyl iodide in 400 ml of DMF was stirred for 18 h at 60°C, and diluted with water to 1.5 liters. The solid was filtered off, dried, and chromatographed (silica gel, eluent chloroform). IR spectrum: 1670, 1740 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 430 nm (3.99). PMR spectrum: 3.80 (s, 3H, N—CH_3), 7.27 (d, 1H, anthraimidazoline 4-H, $J_{4,5}$ = 8 Hz), 7.51 (m, 5H, N—C_6H_5), 7.75 (m, 2H, 8-H and 9-H), 8.09 (d, 1H, 5-H, $J_{5,4}$ = 8 Hz), 8.21 ppm (m, 2H, 7-H and 10-H).

2,3-Dihydro-1-propargyl-3-phenylanthra[1,2-d]imidazole-2,6,11-trione (IIIq). A mixture of 0.5 g (1.5 mmole) of the imidazoline (IIIa), 0.2 ml (2.76 mmole) of propargyl chloride, and 1.6 ml (1.5 mmole) of 5% aqueous KOH in 20 ml of DMSO was stirred for 4 h at 60°C. The product was isolated as for (IIIp), and chromatographed on alumina (eluent benzene). IR spectrum: 1670, 1730 (C=O), 2130 (C≡C), 3250 cm^{-1} (≡C—H). UV spectrum, λ_{max} (log ε): 410 nm (3.89). PMR spectrum: 2.02 (t, 1H, ≡C—H), J = 8 Hz), 5.33 (d, 2H, N—CH_2, J = 8 Hz), 7.17-8.30 ppm (m, 11H arom).

2,3-Dihydro-1-methyl-3-phenyl-5-hydroxyanthra[1,2-d]imidazole-2,6,11-trione (IIIr) was obtained as for (IIIp) in the presence of 5% aqueous KOH. IR spectrum: 1640, 1670, 1740 cm^{-1} (C=O).

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NAPHTHINDOLES. 2*. NAPHTHO[2,3-e]INDOLE-4,9-DIONES AND NAPHTHO[2,3-f]INDOLE-5,10-DIONES

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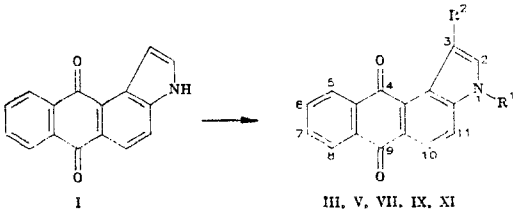
The reactivity of naphtho[2,3-e]indole-4,9-dione and naphtho[2,3-f]indole-5,10-dione towards electrophiles (acylation, azocoupling, and the Mannich and Vilsmeier reactions) has been examined.

In order to assess the reactivity of the previously-synthesized naphtho[2,3-e]indole-4,9-dione (I) and naphtho[2,3-f]indole-5,10-dione (II) [1], we have examined some electrophilic substitution reactions characteristic of indoles, namely acylation, azocoupling, and the Vilsmeier and Mannich reactions. A qualitative comparison of the physicochemical properties of (I) and (II) with indole and some electron-deficient tetracyclic pyrroles such as 3H-pyrrolo[2,3-c]acridine and 3H-pyrrolo[2,3-c]phenothiazine-11,11-dioxide has also been carried out.

The Vilsmeier reaction of (I) and (II) with N,N-dimethylformamide gives 3-formylnaphtho[2,-3-e]indole-4,9-dione (III) and 3-formylnaphtho[2,3-f]indole-5,10-dione (IV) in lower yields (70%) than in the case of indole, but somewhat higher than in the case of pyrroloacridine and pyrrolophenothiazine dioxide [3, 4]. Aminomethylation of (I) and (II) with the crystalline Mannich reagent [5] in DMF at 75°C gives 3-N,N-dimethylaminomethylnaphtho[2,3-e]indole-4,9-dione (V) hydrochloride and 3-N,N-dimethylaminomethylnaphtho[2,3-f]indole-5,10-dione (VI) hydrochloride.



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*For communication 1, see [1].

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